CEPI

Coalition for Epidemic Preparedness Innovations

Preliminary Business Plan

2017-2021



November 2016; version 1

Photo credits: Sean Hawkey

CEPI's value proposition

Epidemics of emerging infectious diseases, such as SARS and Ebola, threaten life, health and prosperity. They are among the world's most pressing health security issues.

We need an insurance policy. Research and development (R&D) to create vaccines could provide one.

CEPI will co-ordinate funding and stimulate R&D for vaccines against emerging infectious diseases. This will avert humanitarian crises, contain loss of life, and limit social and economic disruption.



Børge Brende (Norwegian Ministry of Foreign Affairs): *"Having seen the devastating effects of Ebola on communities and even whole countries with my own eyes, we must do everything we can to prevent infectious disease outbreaks from developing into humanitarian crises in the future"* says Børge Brende, Minister of Foreign Affairs in Norway. *"CEPI is a key, concrete component to develop vaccines in our collective effort to protect humanity from future health crises."*



Jeremy Farrar (Wellcome Trust): *"Vaccines are among the most powerful defenses we have against infectious disease, but the world has failed to tap their potential to protect us all against epidemic threats. We know what many of these threats are and we can develop innovative approaches for those we cannot yet predict. But we need a coordinated, systematic and global approach for developing vaccines against these infections before outbreaks arise. CEPI will provide just such a system, combining the best qualities of the public, private and philanthropic sectors to deliver new vaccines for a safer world."*



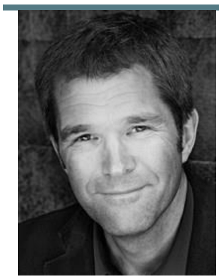
Vijay Raghavan (Government of India): *"Imagine what we could do if we worked together and were prepared when the next Ebola or SARS came along. We could stop disease in its tracks. In India, we have provided high quality vaccines to the world's children, helping control disease in Latin America and Africa, as well as our own country. This is an opportunity to partner globally to advance science and build the level of preparedness that we need today and will need in times to come. Working together is the bedrock of this endeavor. India is ready to commit its science, resources and technical capacity to this challenge."*



Arnaud Bernaert (World Economic Forum): *"The current model to develop and test vaccines is unsustainable. No single organization, government, foundation or manufacturer can address the barriers to epidemic vaccine development alone, yet the threat of emerging infectious disease outbreaks is a lingering reality. CEPI fills a critical global gap and will deliver new vaccines to those who need them the most by maximizing public and private collaboration. As CEPI could become the poster child for such an approach, we at the World Economic Forum are committed to catalyze many more of such impactful partnerships."*



Trevor Mundel (Bill & Melinda Gates Foundation): *"We live in an increasingly interconnected world, and the Ebola and Zika outbreaks have shown we lack the biomedical tools, R&D investment strategies, regulatory frameworks and proactive surveillance systems needed to stop the next pandemic. Many deadly viruses with the potential to erupt into global health crises circulate at the edge of human society. We've encountered these pathogens before, and we can be confident they'll return. That's why the Bill & Melinda Gates Foundation is working in partnership with public and private sector partners to overcome market failures, address technological and regulatory challenges, and accelerate the development of safe and effective vaccines for known and unknown pandemic threats. Through CEPI, coupled with an improved pandemic surveillance system, we can be better prepared for what tomorrow brings."*



John-Arne Røttingen (Interim CEPI CEO): *"The R&D response to the Ebola epidemic in West Africa was both a success and a failure. Never before have industry, government agencies, academia and NGOs collaborated so effectively to plan and conduct more than a dozen clinical vaccine trials in less than a year. But it also showed that the R&D system is not prepared for these threats: we had not done the right research before the epidemic, causing needless delay and loss of life. CEPI will build on the spirit of working together that was ignited by Ebola to create a new R&D system for epidemics that several international panels have demanded. This partnership will give us the new vaccines we need for a safer world."*

Acknowledgements

The review of the Business plan has been informed by discussions during meetings and written comments and feedback from numerous CEPI partners.

We are grateful to all contributors for generously sharing their time and insights to ensure the relevance and quality of this revised version of the Business plan.

List of acronyms

ADM	-	Advanced Development and Manufacturing
ADP	-	Advanced Development Partnership
AMC	-	Advance Market Commitment
AVAREF	-	African Vaccine Regulatory Forum
BARDA	-	The Biomedical Advanced Research and Development Authority
BPO	-	Dedicated Bio preparedness Organization
CEPI	-	Coalition for Epidemic Preparedness Innovation
CIADMs	-	Centers for Innovation in Advanced Development and Manufacturing
CMOs	-	Contract Manufacturing Organizations
COI	-	Conflict of Interest
DCVMN	-	Developing Countries Vaccine Manufacturers Network
EC	-	European Commission
EID	-	Epidemic Infectious Disease
EMA	-	European Medicines Agency
GAVI	-	Gavi, the Vaccine Alliance
GMP	-	Good Manufacturing Practices
IFFim	-	International Finance Facility for Immunization
IMI	-	Innovative Medicines Initiative
JCG	-	Joint Coordination Group
LMICs	-	Low and Middle Income Countries
LSHTM	-	London School of Hygiene and Tropical Medicine

MNC	-	Multinational Corporation
NIPH	-	Norwegian Institute of Public Health
NAM	-	National Academy of Medicine
PDP	-	Performance Designed Products?
PHEIC	-	Public Health Emergency of International Concern
PPCs	-	Preferred Product Characteristics
R&D	–	Research and Development
RfP	-	Requests for Proposal
SAC	-	Scientific Advisory Committee
TPP	-	Target Product Profile
UNSG	-	Secretary-General of the United Nations
US FDA	-	United States Food and Drug Administration
WHO PQ	-	World Health Organization Prequalified Vaccines

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Executive Summary

Epidemics of emerging infectious diseases are a significant and growing threat to life, health, and prosperity. They can arise anywhere at any time, but disproportionately affect low-income countries where needs are often greatest. Recent outbreaks, such as Ebola and SARS, have claimed thousands of lives and cost billions of dollars, both to countries that were directly affected and those that contributed to responding. In a world of denser cities, increased mobility, and ecological change, the disruptive impact of emerging infectious disease is increasing. Ongoing outbreaks of Zika, for example, will pose devastating health and economic impacts for years to come.

These outbreaks have exposed the need for a global mechanism to coordinate research and development for health technologies against epidemic threats. Timely vaccine development can avert global public health emergencies, contain loss of life, and limit the social and economic damage of outbreaks, but the safe and effective vaccines we need aren't being developed well enough, or quickly enough.

CEPI – the Coalition for Epidemic Preparedness Innovations – will tackle the barriers to epidemic vaccine development, advancing safe, effective, and affordable vaccines to contain outbreaks at the earliest possible stage. It will give us the joint global insurance policy we need, helping the populations most at risk and making us all safer.

The Challenge

As the recent SARS, MERS, Ebola and Zika outbreaks demonstrate, new diseases can emerge quickly and unexpectedly. While vaccines are feasible for numerous EIDs, poor commercial prospects and/or risky development pathways stall their development. Experience with Ebola demonstrates that, while it is possible to develop safe and effective vaccines against EIDs in an emergency, the global community cannot continue to rely on *ad-hoc* coalitions and the goodwill of a handful of companies. To ensure robust and effective private sector participation in future outbreaks, industry will require a reliable risk/reward sharing system, a prioritization system for EIDs, and a clear development pathway for emergency-use vaccines.

The Opportunity

CEPI - a global non-profit public-private partnership founded by the Government of Norway, the Government of India, the Bill & Melinda Gates Foundation, the Wellcome Trust and the World Economic Forum - will rationalize and accelerate research and development responses to new outbreaks by coordinating resources of industry, governments, philanthropic organizations and NGOs, prioritizing development goals, and facilitating the advanced development of vaccines for EIDs.

Vision, mission and scope

Vision

Vaccines can prevent outbreaks of emerging infectious diseases from becoming humanitarian crises.

Developing vaccines before epidemics arise will allow the global health community to prevent outbreaks from becoming international public health emergencies. CEPI will prepare vaccine candidates for large efficacy trials and potential emergency deployment in an outbreak. Early intervention will contain loss of life, limit social and economic disruption and protect against future epidemics.

Mission

CEPI will stimulate, finance and co-ordinate vaccine development against emerging infectious diseases with epidemic potential, especially in cases where market incentives alone do not achieve this.

CEPI will coordinate resources from industry, academia, governments, philanthropies, and NGOs to facilitate the advanced development of vaccines for emerging infectious diseases with epidemic potential (EIDs). CEPI will focus on development and manufacturing platforms that can be used against a range of known and unknown EIDs.

Scope

CEPI takes an end-to-end approach to vaccine development, with an initial focus on two priorities: 1. moving new vaccines through late preclinical studies to proof of concept and safety in humans, and 2. supporting vaccine platforms that can be rapidly deployed against known and unknown pathogens.

CEPI will assess the feasibility of vaccine development against priority pathogens identified by the WHO R&D blueprint and other processes and fund vaccine preparedness efforts accordingly. CEPI will fund and coordinate activities including late-stage preclinical development, clinical Phase I and II safety and efficacy trials with pilot stockpiles and regulatory pathway and Phase III clinical trial planning for outbreaks. CEPI will also coordinate with independent early discovery groups, R&D funders, and vaccine procurement and delivery organizations such as Gavi.

Strategic objectives & outputs

1

Preparedness

Advance late-stage EID vaccine development to enable testing in the initial stages of an outbreak

Expected Output 1: By 2021, CEPI will have advanced four to six vaccine candidates against two to three priority EIDs to proof of concept and ready for Phase III; partnering with industry to ensure sufficient global vaccine development and manufacturing capacity.

2

Response speed

Build technical and institutional platforms to accelerate research, development, manufacturing, and clinical evaluation in an outbreak

Expected Output 2: By 2021, CEPI will establish rapid response R&D capabilities and will test and refine these systems in the event of an epidemic.

3

Market predictability

Secure industry participation through partnerships that share the risks and benefits of vaccine development

Expected Output 3: By 2021, CEPI will have expanded the number and types of financing and incentive mechanisms directly supported or facilitated by CEPI, increasing global capabilities for EID vaccine development and manufacturing worldwide.

4

Equity

Support the long-term development of regional capabilities for EID vaccine preparedness

Expected Output 4: By 2021, improved regional capabilities including in developing countries, will have been promoted to support CEPI's core business model of advanced EID vaccine development and manufacturing, coordinated through partner networks in Asia, Africa and South America.

Investments

The gap

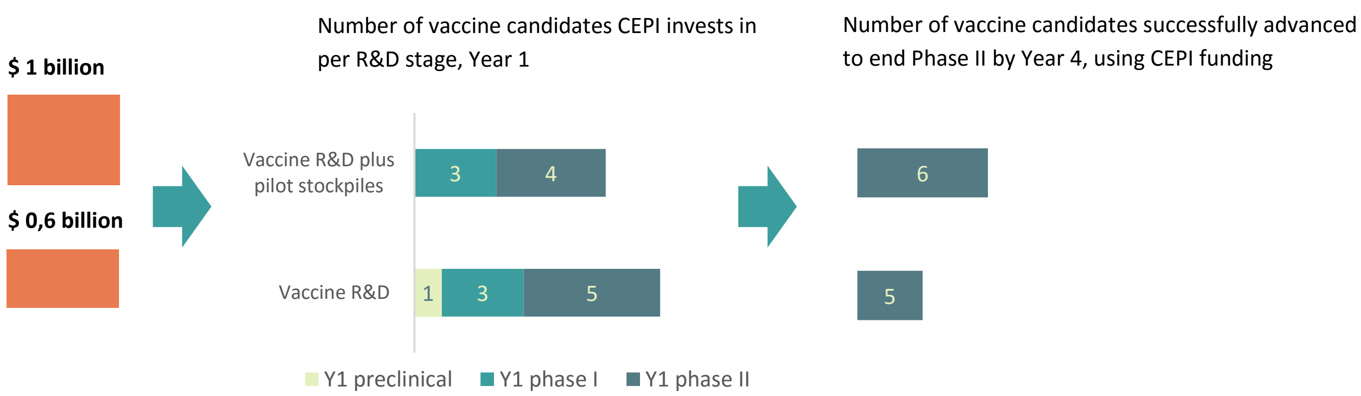
The advancement of vaccine candidates to proof of concept against 10 WHO R&D Blueprint-listed pathogens can cost at least USD 0.6 billion over five years, and it can reach up to USD 3.7 billion, including costs of pilot manufacturing and stockpiles.

Estimates to advance pipelines with active vaccine candidates for 10 WHO R&D Blueprint pathogens to end of Phase II trials within five years vary depending on the complexity of the vaccine technology, pilot plant requirements, and other manufacturing cost variants.

The CEPI target

CEPI should invest USD 0.6 - 1 billion today in order to advance four to six vaccine candidates to proof of concept in five years.

These estimates are based on currently known vaccine pipeline costs, expected CEPI budget constraints, and a portfolio target of two to three WHO R&D Blueprint listed pathogens over 5 years. With investments of up to USD 1 billion, CEPI could fill over a quarter of the global funding gap for emerging infectious diseases of epidemic potential. Given the risks of R&D failure, CEPI estimates that it would need to invest in seven to nine vaccine candidates today (at different stages of preclinical or early clinical development) in order to achieve its five-year portfolio target.



Partnership & organization model

The partnership model

CEPI is building capabilities through a mix of partnership models.

At its core, CEPI includes an Advanced Development Partnership (ADP) consisting of a network of newly set up or existing and contracted Advanced Development and Manufacturing (ADM) organizations to develop vaccines against CEPI pathogens up to proof of concept and pilot scale manufacture.

Through joint coordination with others, CEPI will fill R&D gaps as needed and coordinate with other entities to set priorities, pathogen-specific road maps, plans to accelerate clinical testing and approval of products in epidemic situations. CEPI will also coordinate with others on vaccine stockpiling and distribution.

Operating model startup phase

The CEPI Board will govern CEPI. A management team led by the CEO will coordinate day-to-day operations through a core Secretariat node in Norway and other nodes with distributed capacities worldwide.

A Scientific Advisory Committee (SAC) will advise CEPI on scientific matters and a Joint Coordination Group (JCG) coordinates CEPI's activities with other actors across the end-to-end spectrum of vaccine R&D response and preparedness planning.

Financing model

CEPI seeks multi-year donor commitments to satisfy core financing needs, as well as targeted investments directed specifically to CEPI priority targets through a multi-source financing model.

CEPI will source and use financing around four key principles: secure support from the broadest possible base of funders; long term, predictable financing; complementary and new financing; fit-for-purpose financing.

Operating principles

Three operating principles serve as the foundation of CEPI's strategic and business framework:

Equitable access	Global access arrangements will be negotiated in contracts between CEPI and vaccine developers to ensure affordability and availability in Low and Middle Income Countries (LMICs). The price of vaccines developed through or with the support of CEPI should not be a barrier to access.
Cost coverage	Vaccine developers who contribute with dedicated capacities should be reimbursed for their direct and indirect costs.
Shared benefits	It is anticipated that vaccines developed with CEPI support will not be profitable. In the event that a vaccine developed with CEPI support does develop economic value, agreements between CEPI and the vaccine developer will ensure either that CEPI's investment is reimbursed or that the economic value is shared through royalties or other risk sharing agreements. Any rewards that accrue to vaccine developers should be proportionate to the level of risk undertaken and to the nature of the R&D, infrastructure, IP or other contributions a developer has made.

Introduction

The 2014 Ebola viral disease (Ebola) outbreak in West Africa underscored the need to invest in medical countermeasures for epidemic infectious diseases that are characterized by limited market potential (EIDs). A failure to invest in these countermeasures will result in the loss of human lives, the devastation of national economies, and more humanitarian crises.

In her capacity as Chair of G7 in 2015, Chancellor Merkel took the lead on preventing such outbreaks in the future. Bill Gates chaired a meeting of experts in March 2015, which succinctly outlined the Research and Development (R&D) agenda. Subsequently, a number of independent reviews have documented the failures of the international response and set out recommendations to prevent such outbreaks in the future (see background section below).

These reviews outline a broad set of required actions including strengthening surveillance and response capabilities at national and global level and strengthening R&D responses, including the development of effective vaccines. Governments are starting to commit to these recommendations - most recently at the G7 Summit in Japan - to mitigate the inaction that had also followed previous outbreaks such as that of SARS 2002/03, H5N1 in 2005 and H1N1 in 2009.

Based on consultations in the global health community there is broad recognition that there are unmet gaps in the current architecture to respond to the R&D needs for emerging infectious diseases with epidemic potential. This gap requires a new dedicated global initiative. The Coalition for Epidemic Preparedness Innovation (CEPI) sets out to fill that gap. This document sets out the strategic and business framework for CEPI.

Background

EIDs pose a growing threat to global health security in a world of higher population density, increased mobility and ecological changes. Recent EID outbreaks like Ebola, have claimed thousands of lives and billions of US dollars in losses for economies that were both directly and indirectly affected by the outbreak. And yet, these outbreaks have not been as damaging as they could have been had they surfaced in a large metropolitan area.

Following the 2000 Millennium Development Goals, government and philanthropic funding has built a growing community of product developers with pipelines for new vaccines, diagnostics and drugs for many high-burden diseases that primarily affect citizens living in the poorest countries. However, effective biomedical tools such as vaccines and drugs are almost entirely lacking for EIDs despite their known epidemic potential. EIDs are characterized by limited market potential, and planning for these diseases is especially challenging due to the sporadic nature of their emergence and re-emergence. Better R&D preparedness – through new or improved biomedical products, better R&D response speed, proactive planning for clinical testing, regulatory approval and delivery– is urgently needed.

As the recent SARS, MERS, Ebola, and Zika outbreaks demonstrate, new diseases can emerge quickly and unexpectedly. However, biomedical R&D can be highly complex, lengthy, rigid and costly. Devising new ways to accelerate development times is both difficult and necessary. New and better coordinated funding is essential to build and sustain an EID countermeasure

program. Funding, however, is not enough. To succeed, this program must pair new funds with new institutional and technical platforms to improve the speed of development.

TEXTBOX 1: WHO R&D Blueprint – top emerging pathogens likely to cause severe outbreak in the near future. May 2016

Diseases to be urgently addressed under the R&D blueprint:

- Crimean Congo Hemorrhagic fever virus
- Filovirus diseases (Ebola and Marburg)
- Highly pathogenic emerging coronaviruses relevant to humans (MERS Co-V, SARS)
- Lassa fever virus
- Nipah virus
- Rift Valley fever virus
- *a new severe infectious disease

Serious diseases necessitating further action as soon as possible:

- Chikungunya
- Severe fever with thrombocytopenia syndrome
- Congenital abnormalities and other neurological complications associated with Zika virus

See Annex 1 for priority pathogens by different sources and Annex 2 for disease characteristics and vaccine pipeline.

Vaccines – CEPI's focus today – are an important tool in our effort to protect the world against EID outbreaks. Feasible vaccine candidates exist for some of the EIDs within CEPI's initial scope (see text box and annexes 1 and 2). When this is the case, it is possible, as we saw in the Ebola outbreak, to develop vaccines quickly, even in extremely challenging conditions. All major post-Ebola reports – WHO, LSHTM / Harvard / Lancet, NAM / Global Health Risks Framework, and UNSG High-level Panel (Moon, Sridhar et al. 2015, World Health Organization 2015, United Nations Secretary General 2016) – agree however, that this process must be reformed. The current model, which relies on *ad-hoc* initiatives and the good will of a handful of biopharmaceutical companies, is insufficient for several reasons:

- **The pipeline is weak for most EIDs.** Unlike Ebola, which had several candidate vaccines ready to go into Phase I trials at the point of the 2014 outbreak, this is not the case for many other EIDs. If left as is, EIDs can spread faster than our ability to develop vaccines and drugs. Even with efficacy demonstrated in animal models, individual preclinical vaccine development projects have a 30% chance of becoming a licensed product. R&D pipelines need to be more robust to ensure a positive outcome.
- **Clinical trials suffer unnecessary administrative delays,** even when products are ready for clinical testing. Efficacy trials for Ebola could have started 6 months earlier if the Public Health Emergency of International Concern (PHEIC) had been declared earlier, if we had already conducted phase 1 and 2 trials, or if we had already developed pre-agreed regulatory and data sharing pathways, clinical trial design protocols. Proactive planning

and the implementation of an intermediate alert for PHEIC can accelerate development times significantly.

- ***Ad-hoc* initiatives for vaccine development are fragmented and unpredictable**. Most R&D for development of EID vaccines is publicly funded and performed by government institutions and academia. These operate without a coordinated global mechanism to turn promising ideas into safe and effective public health interventions, and therefore EID vaccine development tends to be left to *ad-hoc* initiatives in non-epidemic periods. On the other hand, it is multinational vaccine manufacturers who are called upon during international crises, due to their organisational capabilities for developing vaccines for profitable markets. Some companies arguably spent hundreds of millions of dollars in Ebola vaccine development, which is unprecedented in the global health space. However, there is no guarantee of a similar risk-taking outcome in future. To build a sustainable system of R&D preparedness, the global health community needs to create better mechanisms for sharing risks and benefits with industry and to become a better matchmaker between the EID research community and industry.
- **Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks.** Countries in the so-called global hot spots for infectious disease outbreaks often do not have the resources to invest in research to prevent endemic infectious diseases. There is no mechanism for vaccine development addressing global epidemic risks beyond national borders. Numerous funders, along with developers, responded quickly to the West African Ebola epidemic with funds and contributions to support the clinical testing of vaccines and drugs, amounting to US$ 165m for 2014 alone, according to the G-FINDER survey on neglected disease R&D investments. But biomedical product development can take 10 to 15 years and over one billion U.S. dollars to reach the market. This endeavour requires long term, predictable funding.
- **The global health community is operating without an insurance policy against a growing threat from EIDs.** The economic cost of epidemics is disruptive: US$ 2.2 billion for Ebola; US$ 54 billion for SARS; US$ 30 billion expected annual value of pandemic risk, according to the WHO R&D Blueprint for action to prevent epidemics – all which is often much larger than the cost of vaccine or drug development. Advancing R&D preparedness and proactive R&D response planning is a sound investment in global health security and in preventing infectious disease outbreaks from having detrimental effects on national economies, health and educational systems.

The CEPI response

Recognizing the urgent need for a new approach to EID vaccine development, leading figures from governments, foundations, industry and civil society proposed a coalition for proactive R&D during the Annual Meeting of the World Economic Forum in Davos in January 2016. Since then, representatives from industry, governments, foundations, regulators, intergovernmental organisations, such as WHO and civil society organisations, have been closely collaborating to create a Coalition for Epidemic Preparedness Innovations (CEPI). CEPI has been separate from (but complementary to and strongly informed by) the WHO-led process to develop an R&D Blueprint for emergencies.

During its initiation phase (January 2016 – June 2016), CEPI has consisted of a stakeholder group and a project management group that set up expert task teams to consider issues such as

pathogen prioritisation, clinical development, manufacturing capacity and regulatory pathways, potential models for partnership, funding needs, resource mobilization and shared risk/reward arrangements between sectors. The three task teams recommended that CEPI focuses its investments on vaccine development from preclinical to clinical Phase II development with pilot stockpiles and that it makes use of rapid response technology platforms where possible. The task teams suggested that CEPI should coordinate vaccine development from an end-to-end perspective including alignment around plans for clinical Phase III studies, regulatory approval pathways and procurement should an epidemic occur.

Building on the recommendations of these groups, CEPI has now transitioned into a start-up phase (July 2016 – December 2017) and is evolving through a multi-sectorial dialogue between its members. A temporary structure has been designed to ensure the start of implementation and also that all stakeholders can contribute their perspectives on CEPI's permanent organizational structure and governance. To this purpose, an interim Secretariat of CEPI is being hosted at the Norwegian Institute of Public Health (NIPH), and a legal entity has been set up in the form of an international non-profit association. The founders of the association - the Gates Foundation, the World Economic Forum, the Wellcome Trust, India's Department of Biotechnology, and the Government of Norway – are working closely with the interim Secretariat to manage the operational aspects of CEPI. Preparations are underway so that CEPI's official launch will take place at the World Economic Forum in January 2017.

Situation analysis

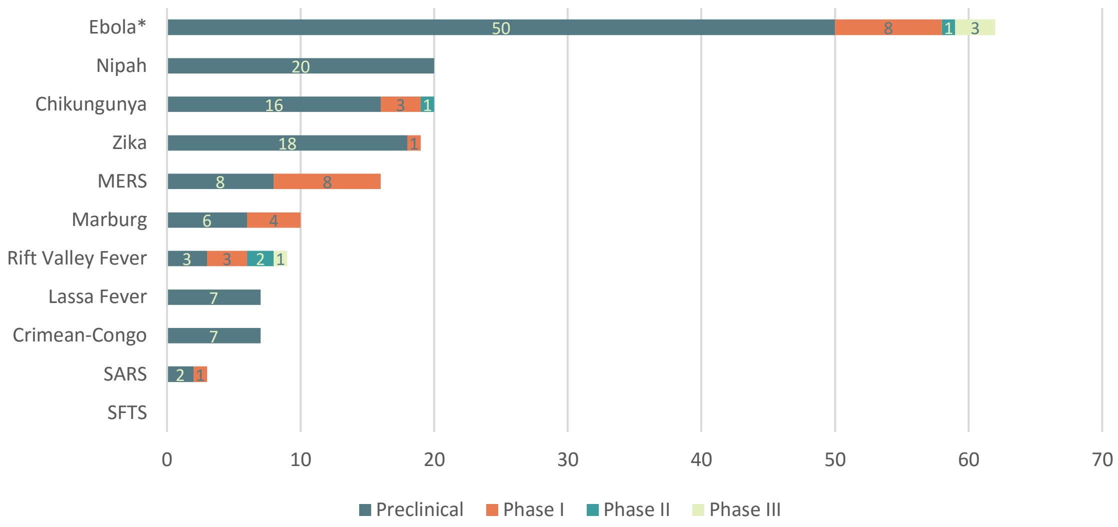
Feasible vaccine candidates exist for a majority of the priority pathogens highlighted by WHO. Vaccine developers have the capacity to push these candidates through the pipeline, although there is little commercial incentive to do so. Moreover, clinical development and regulatory norms are not easily adapted to epidemic contexts.

Opportunities

While vaccines are feasible for numerous EIDs listed in the WHO R&D Blueprint priority list, poor commercial prospects and/or a risky development pathway have stalled their clinical testing and transition into becoming safe and effective public health tools. Experience with Ebola, however, demonstrates that it is possible to advance the clinical development of safe and effective vaccines against EIDs in an emergency. The rVSV-ZEBOV Ebola vaccine trial, conducted in Guinea by a consortium of WHO, MSF, Norwegian Institute of Public Health and MoH of Guinea, produced an Ebola vaccine candidate that was highly effective in preventing Ebola. The vaccine had previously been developed by the Public Health Agency of Canada, advanced by NewLink Genetics and acquired and manufactured for clinical testing and distribution by Merck. Two other vaccine candidates (GlaxoSmithKline's ChAd3.EBOZ; and Ad26.ZEBOV +and MVA-BN-Filo by Janssen (J&J) and Bavarian Nordic) have progressed beyond Phase I with trials held in multiple West African countries, Europe and North America. These collaborative efforts by pharmaceutical companies, regulatory agencies, governments, academia, and NGOs demonstrated that vaccine development timelines can be compressed and novel clinical development and regulatory pathways can be applied to protect people from emerging infections.

As Figure 1 demonstrates, current vaccine R&D pipelines vary in depth and breadth by pathogen. The most active pipeline (i.e. total number of vaccine R&D projects) is for Ebola, followed by Chikungunya, Nipah Virus, Zika Virus, MERS, Marburg, Rift Valley Fever, Crimean Congo Haemorrhagic Fever, Lassa Fever and SARS. No vaccine R&D projects against SFTS have been identified to date. Phase III projects are being undertaken only for Ebola and RVF, whereas Phase II projects are being undertaken for Ebola, Chikungunya and RVF. Phase I projects are being undertaken for a number of EIDs (Ebola, Chikungunya, Zika, MERS, Marburg, Rift Valley Fever, SARS). Some EIDs (Nipah, Crimean Congo Haemorrhagic Fever and Lassa Fever) have no projects beyond the preclinical stage. Details on vaccine pipelines per pathogen are provided in Annex 1.

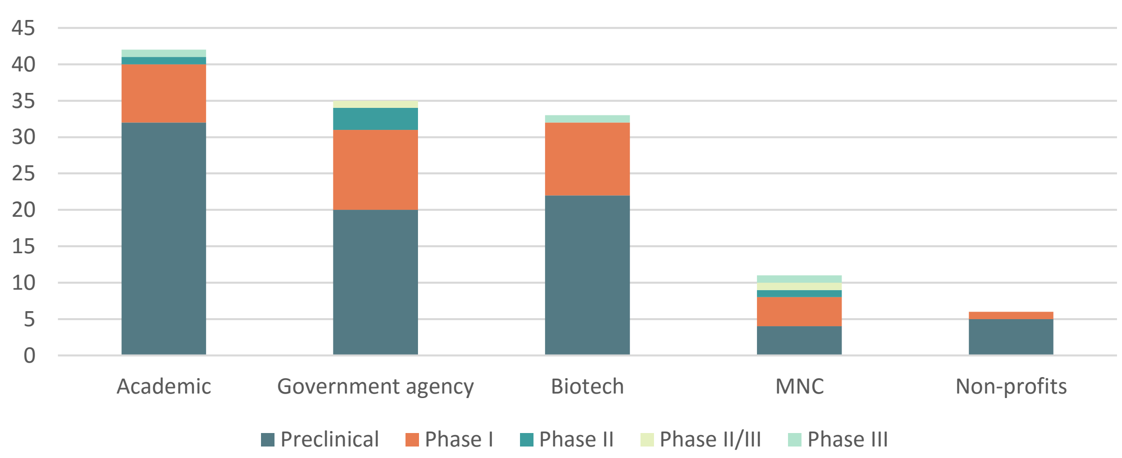
FIGURE 1: VACCINE PIPELINES FOR PRIORITY PATHOGENS INCLUDED IN THE WHO R&D BLUEPRINT LIST AS AT MID-2016



Sources: reports from CEPI task teams, literature, clinicaltrials.gov, NIH project reporter database (*preclinical estimated; Phase I numbers include prime-boost regimens and novel candidates)

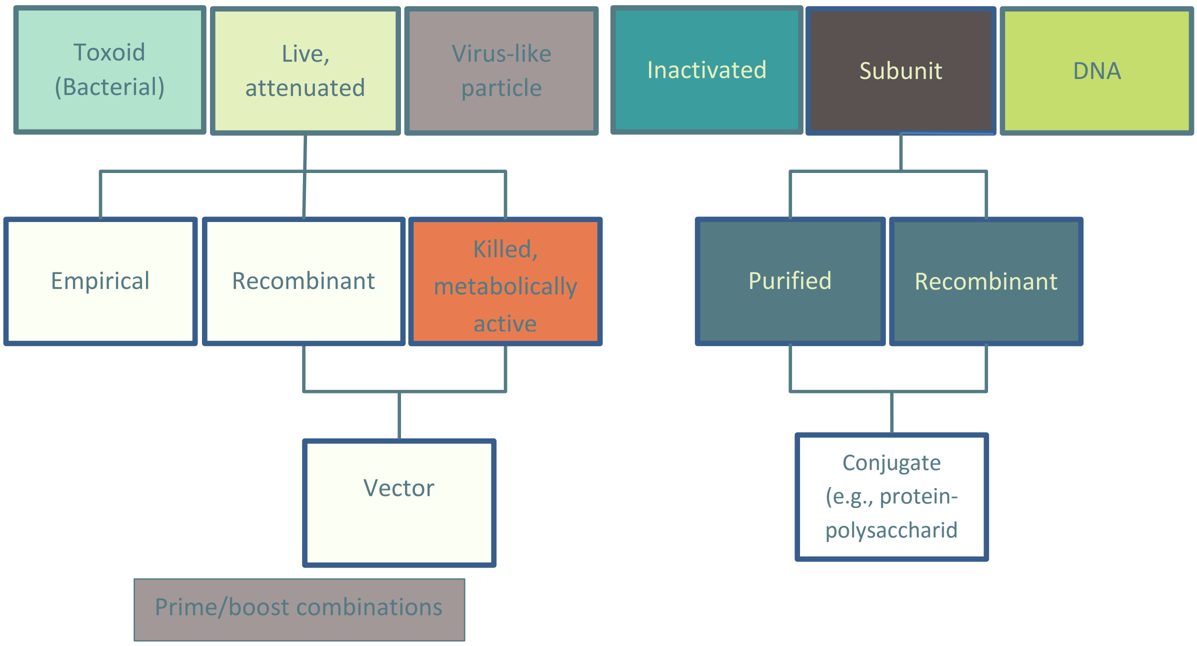
The above pipeline (see Figure 1) represents the collective work of government health research agencies, academic research institutions, biotechnology companies (biotechs), multinational vaccine manufacturers, and non-profit organizations as of mid- 2016. Most of the researchers involved in this vaccine R&D for the WHO priority diseases are employed in academia, government agencies and biotech companies (see Figure 2). This is relevant for targeting the funding for these diseases, and for identifying how to best match existing human capacities in this field with clinical testing and manufacturing capabilities within the large multinational vaccine manufacturers.

FIGURE 2: RESEARCHERS AND DEVELOPERS INVOLVED IN VACCINE PIPELINES FOR DISEASES INCLUDED IN THE WHO R&D BLUEPRINT LIST



Manufacturing capability and capacity for vaccines has always been a critical bottleneck in handling epidemic events, but major vaccine manufacturers can drive pipelines forward. Human vaccines are manufactured using a variety of technology platforms, which make it difficult to develop standardized process architectures and facility designs for their production (see Figure 3). Manufacturing cycle times and quality control can be difficult, costly, and time consuming. Facilities supporting these platforms are unlikely to become available for more than one product at a time, and are rarely dedicated to potential epidemic events alone. However, some companies are transitioning to more flexible manufacturing platforms that lower capital and operational costs, while accelerating response times. This trend toward flexible manufacturing will build industry capacity to support CEPI's mission. While some expertise for existing platforms is present in the Developing Countries Vaccine Manufacturers Network (DCVMN), industry expertise in novel platforms is concentrated in a handful of multinational biopharmaceutical companies.

FIGURE 3: EXAMPLES OF CURRENT TECHNOLOGIES AVAILABLE FOR VACCINE PRODUCTION*



*Graphic taken from Pralong et al (2014) 'Paradigm shift for vaccine manufacturing facilities: The next generation of flexible, modular facilities' Engineering in Life Sciences. Volume 14, Issue 3. May 2014 . Pages 244–253

Challenges

EID outbreaks require synergistic approaches to early priority pathogen identification and a combination of proactive (just-in-case) and fast-tracked (just-in-time) vaccine development. Transmission of pathogens can emerge rapidly during outbreaks. But vaccines take years to develop. Very few outbreaks can be predicted, however pathogens associated with epidemic disease can be identified early on. Effective use of vaccines as public health tools to prevent, limit, or contain outbreaks requires early identification of priority pathogens linked with a combination of proactive and fast-tracked vaccine development prior to and in response to epidemics respectively.

Incentives are lacking to motivate greater industry engagement. For most EID vaccines, volumes are too small, and the development pathway and market is too uncertain to justify substantial private sector investment. Nevertheless, when a disease begins to spread more widely, as Ebola did in 2014, companies began to contribute to vaccine development efforts at their own risk and at the expense of pursing other projects. Due to the compressed regulatory approval timeline for Ebola, advance agreements that indemnities would be provided were needed to protect product developers from losses if any of their products proved unsafe in clinical trials or if side effects emerge in the future. No such global agreement is in place, however. Prior to the epidemic, the US government had single-handedly funded the bulk of Ebola R&D when other investments worldwide had been virtually non-existent. The classification of the disease as a 'category A priority pathogen' and health security concerns due to bioterrorism threats had encouraged significant R&D funding by the US government in the past 15 years, despite an extremely small global market for Ebola drugs or vaccines. Other EIDs, such as Zika, do not benefit from public funding to the same degree and their pipelines for new vaccines and drugs reflect these different priorities. A prioritization system for EIDs, a reliable reward system, and a clear development pathway are required to overcome industry's reluctance to participate in future EID development projects.

Clinical & regulatory pathways are not easily adaptable to epidemic contexts. The process of developing a vaccine is complex, partly due to safety considerations. This process becomes even more complex in an emergency when some decisions must be made with limited data. The FDA and EMA collectively have over 17 different procedures for accelerated and emergency use. Regulatory requirements can differ by region and few regulatory agencies are generally prepared to approve products swiftly, especially if developed on novel technology platforms. As it stands, outbreaks are likely to occur in regions with less regulatory capacity and weaker regulatory regime. Harmonizing emergency regulatory procedures into a more predictable framework would accelerate speed and efficiency of vaccine development during outbreaks. Early engagement with regulatory authorities will be crucial in this process.

CEPI Opportunity

CEPI is in a unique position today to have partnered with experienced vaccine manufactures with global reach and to have brought together experts, funders, regulators, and governments to address vaccine preparedness goals in the event of global public health emergencies. CEPI has accumulated a breadth and depth of expertise through its three Task Teams and benefited from the evidence generated through the WHO R&D Blueprint process.

Financing vaccine development is an essential first step, but CEPI will not succeed unless it builds an integrated partnership framework for product development.

Strengths

CEPI is in a unique position today to have already partnered with experienced vaccine manufacturers with global reach who have been committed to the CEPI mission since its inception. Leveraging the know-how of leading global vaccine manufacturers and biotechs is crucial to achieving CEPI's goals. The WHO R&D blueprint process has identified several platform technology proposals for human vaccine development that have the potential to rapidly develop vaccines against known or unknown pathogens in the event of an epidemic. Two of these are fully owned (see textbox 2). Six MNCs and partners of the World Economic Forum – GlaxoSmithKline, Merck, Sanofi, Johnson & Johnson, Pfizer, Takeda – are already actively partnering with CEPI, assessing what platform technologies, staff and manufacturing facilities they can contribute. These range from dedicated product development facilities to project-based partnerships utilising their existing biosafety facilities.

CEPI could leverage EID research expertise and public facilities already active in the field. Existing government or non-profit organisations in the field of EID vaccine research have offered access to expertise and manufacturing capabilities. These facilities can develop candidates to a pre-specified clinical end point and license the candidate out to large-scale producers in the event of an outbreak. The Biomedical Advanced Research and Development Authority (BARDA), in particular, has suggested that its Centers for Innovation in Advanced Development and Manufacturing (CIADMs) could work with CEPI partners to produce vaccines using one of their supported platforms.

TEXTBOX 2: WHO R&D Blueprint – Top 5 vaccine–related technology platform proposals according to a WHO consultations process

1. *Dedicated Biopreparedness Organization (BPO)*. **Lead entity**: GlaxoSmithKline. **Vaccine platforms proposed**: Adenovirus, DNA, RNA, recombinant proteins+ adjuvants, conjugates.

2. *Janssen Vaccines – Jenner Institute complementary Vaccines Platform Technologies.* **Lead entities**: Janssen (J&J); Jenner Institute Oxford, UK. **Platforms proposed**: MVA, Adenovirus, Recombinant protein VLP, Whole inactivated virus.

3. *Modified Vaccinia Ankara Platform Partnership (Mva-Pp).* **Lead entities**: Bavarian Nordic; German Centre for Infection Control (DZIF); Public Health England. **Platform proposed**: MVA.

4. *ADEPT platform - vaccines, diagnostics, small molecules, immunotherapies, non-clinical testing, clinical testing.* **Lead entity**: USAMRIID, US. **Platforms proposed**: VSV, DNA, RNA (GSK).

5. *PREMVac: Pre-epidemic Readiness for Emerging diseases through Measles vectored Vaccine platform*. **Lead entities**: Institut Pasteur, France; Thermis Bioscience, Austria; EpiVax, US; CIC, France; CNRFP, Burkina Faso. **Platform proposed**: Measles virus vector.

A number of biotechs could add value to CEPI's portfolio via discovery, development and contract manufacturing capabilities worldwide. Preliminary scoping of vaccine R&D and manufacturing capabilities by CEPI partners has identified small to medium-sized commercial vaccine companies, biotechs and contract manufacturing organizations (CMOs) working on priority targets, either with known capabilities in place or with pipeline products and known technologies. These companies could research and develop vaccine candidates, collaborate with major vaccine developers as technical partners, or manufacture vaccines at a pilot scale in cases where their supported platforms are qualified.

CEPI has already accumulated a breadth and depth of expertise through its three Task Teams. Over 70 governmental, industrial, civil society, academic and international organization representatives and experts have gathered through a series of interactive workshops and teleconferences to develop proposals for the science and regulation, partnership models and financing considerations of CEPI. These individuals represent the world's leading thinkers and experts on clinical development and trials, vaccine manufacturing, regulation, vaccine costing, financing and supply in developing countries. Task team 1 addressed i) prioritization of pathogens, ii) clinical development, iii) manufacturing and stockpiling and iv) regulatory and legal pathways. Task team 2 identified appropriate partnership models for financing and coordinating EID vaccine R&D. Task team 3 explored different mechanisms that could be included in the CEPI financing facility and outlined recommendations for further development.

These task teams identified several key factors that will drive CEPI's ability to be a successful initiative with a lasting impact. These include establishing a robust prioritization framework; an

ability to identify and address causes of slow R&D responses encountered in previous epidemics; address private sector risks and incentives; build manufacturing capacity; establish clear operating principles for a multi-sectoral partnership structure to finance and coordinate EID vaccine R&D from end to end; and establish a predictable and sustainable financial base.

CEPI has benefited from the evidence base and recommendations generated through the WHO R&D Blueprint process. Ever since the Ebola epidemic, the WHO has proactively undertaken a set of important functions based on its roles and responsibilities as the global normative body of health to design a new R&D blueprint and emergency response framework to EIDs. This includes pathogen prioritization, product requirements and roadmap setting, regulatory coordination, and platform technology assessments. This wealth of evidence and analysis informs CEPI's approach to prioritization and coordination. Collaboration between WHO and CEPI leverages the strengths of each partner from the outset, avoids duplication, and maximises complementarity.

CEPI's founding organizations have been catalytic in the start-up process. Since inception, five entities have championed the CEPI start-up process: the governments of Norway and India, the Wellcome Trust, the Bill & Melinda Gates Foundation, and the World Economic Forum. Collectively, they have gathered leading experts and institutions and coordinated the operational aspects of CEPI.

Limitations

LMIC representatives from several emerging economies have been actively involved in the CEPI process so far, including representatives from Brazil, India and South Africa. Going forward, LMIC regulators and R&D implementers need a more active voice in CEPI

Textbox 3: Preparing for the next Zika

Over the last decade, the US government has built a system of institutions and incentives to develop medical countermeasures for biodefense and pandemic preparedness. Two elements of the US approach – mechanisms to coordinate stakeholders and to incubate new product development - could be adapted to a global effort to develop vaccines for EID. A third element - building institutional and technical platforms to improve speed- must be expanded to address future outbreaks more effectively.

1. *Coordinate stakeholders*
   A multi-agency steering committee, the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), prioritizes development targets and coordinates federal resources to achieve these targets.
2. *Incubate new product development*
   A single agency (BARDA) manages a portfolio of new development projects and provides individualized, hands-on technical, managerial and regulatory assistance to industry partners that require assistance. BARDA also provides core services such as animal study and clinical trial networks, advanced development and manufacturing facilities and fill-finish networks to prepare bulk products for distribution.
3. *Build technical and institutional platforms to improve speed*
   Vaccine discovery and development platforms could dramatically reduce development times. Building and validating these platforms should be a research priority for a global EID vaccine initiative. This initiative should also build generic legal, administrative and capacity building measures to facilitate research in an emergency.

Hoyt, K., Hatchett, R., "Preparing for the next Zika" Nature

deliberations as well. CEPI's formal governance body will include representatives from both LICs and MICs to ensure acceptance and appropriate implementation in regions where EID outbreaks are more likely to occur.

Mobilizing and directing funds for R&D is essential, but CEPI go one step further by building an integrated framework for product development. Experience from US biodefense and pandemic preparedness efforts, as well as recent global R&D response efforts to EIDs, suggests that effective cross-sector coordination will require dedicated resources.

How can CEPI address the challenges and seize opportunities?

As these external and internal assessments demonstrate, CEPI can leverage numerous assets to serve its mission over the next several years. To succeed however, CEPI must:

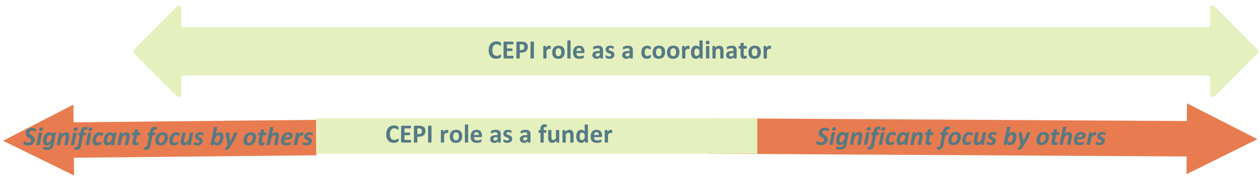
- Establish a common understanding of its mission and principles to align financial and political capital for co-funding and coordination
- Identify its key priorities and investment plans
- Establish predictable funding and clear risk/benefit sharing arrangements with industry (including but not limited to the six MNC's involved in the dialogue so far) in order to fully harness MNC and Biotech capabilities for vaccine development and manufacturing
- Continue to attract and retain top experts in related fields
- Leverage the WHO evidence base and capabilities on clinical and regulatory coordination and ensure complementarity with WHO R&D Blueprint directions

Strategic Framework

Taking an end-to-end coordination approach from vaccine discovery to application, CEPI will focus its investments on essential gaps in product development. Initially, CEPI will focus on 1. late preclinical to proof of principle in humans and 2. the development of platforms that can be used for rapid vaccine development against known and unknown pathogens.

In order to achieve its mission in an efficient manner CEPI will work in partnership with the vaccine industry through innovative mechanisms, regulatory agencies, WHO, R&D partners, and vaccine procurers such as UNICEF Supply Division and Gavi.

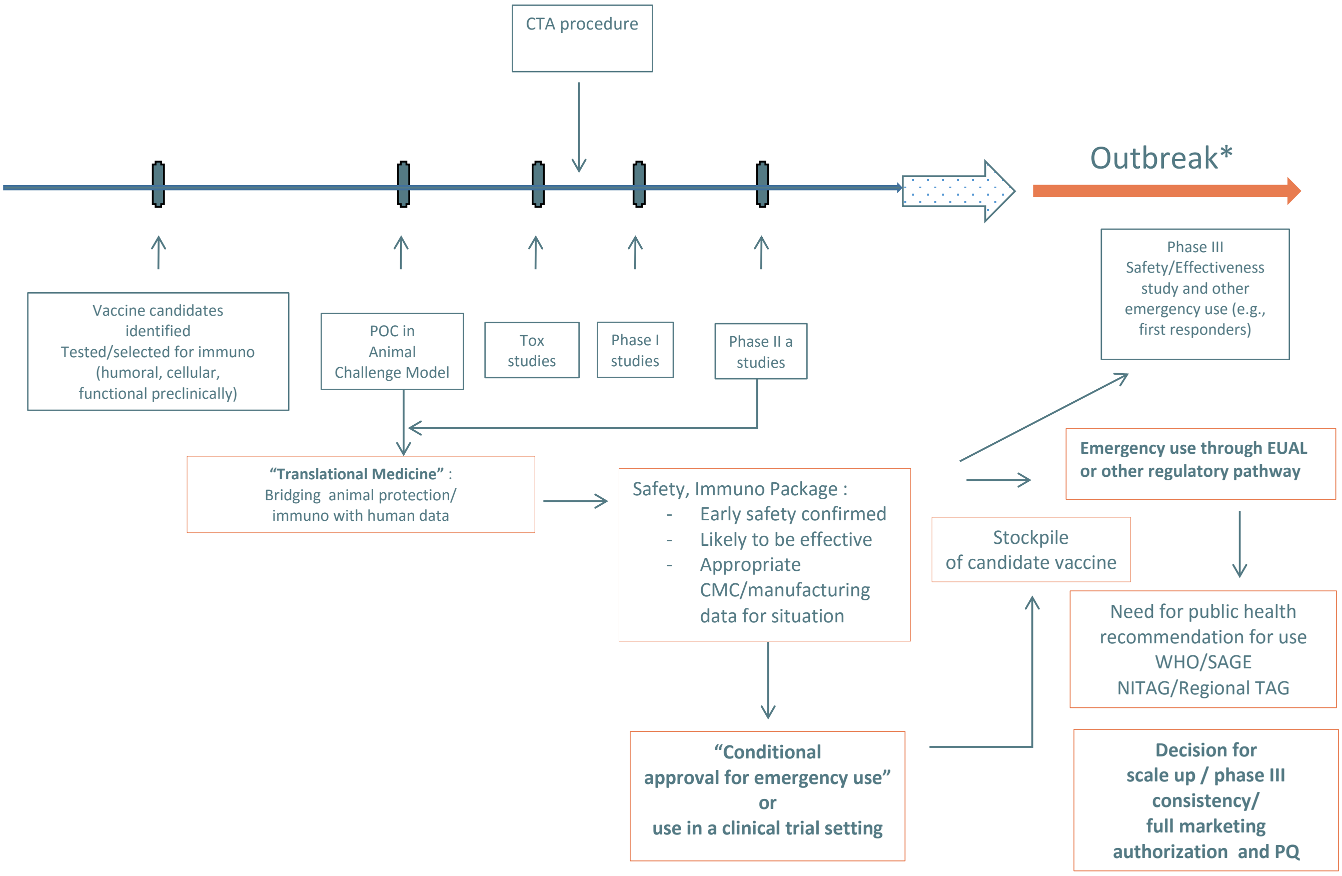
FIGURE 4: CEPI SCOPE AND FIT WITH OTHER INITIATIVES



	1 Discovery	2 Development/ Licensure	3 Manufacturing	4 Delivery/Stockpiling
Current Stakeholders	• Academia • Governments • WT/NIH • GLOPID-R • Industry • Regulators • Biotech	• Industry • National Governments • Regulators • Bill and Melinda Gates Foundation • BARDA/DTRA etc. • WHO • Biotech • PDPs	• Industry • BARDA • CMOs • Regulators • National • Governments • WHO	• GAVI • UNICEF • PAHO • National Governments • WHO • Industry • Pandemic Emergency Facility (World Bank)

There are already many actors in the "end to end space" of vaccine funding and R&D implementation and there is broad agreement that CEPI should avoid duplication and focus funding on the critical gap i.e. the lack of capability to move vaccine candidates from the preclinical stage through to proof of principle (see Figure 4). However, this is not simply a question of funding the development activities required for proof of principle. It also requires CEPI to coordinate activities between R&D and regulatory pathways, ensuring that a vaccine candidate can be successfully deployed in the event of an outbreak, supported by regulatory advice along critical checkpoints (see Figure 5).

FIGURE 5: R&D AND REGULATORY FLOW PATH AND KEY CHECKPOINTS FOR CEPI ALONG THIS CONTINUUM



CEPI will focus on two fundamental strategic objectives (SOs) in order to demonstrate the capacity to deliver on its promise:

- **SO1 – Preparedness**: advance late-stage EID vaccine development to enable testing in the initial stages of an outbreak
- **SO2 – R&D response speed**: build technical and institutional platforms to accelerate research, development, manufacturing, and evaluation in an outbreak

CEPI will also focus on two essential means-to-end SOs in order to ensure sustainability of its strategic partnership approach:

- **SO3 – Market predictability**: secure industry participation through partnerships that share the risks and benefits of vaccine development
- **SO4 – Equity**: support the long-term development of regional capabilities for EID vaccine preparedness

Finally, CEPI will focus on cross-cutting to ensure success of its strategy implementation:

- **SO5 – Cross-cutting**: build integrated planning tools and sustain investments for end-to-end capabilities through joint coordination and management

To achieve these strategic objectives, CEPI will initially focus on a small number of candidate vaccines, including those with the highest probability of success. CEPI will draw on a wide variety of platform technologies and leverage diversity of industry partners, particularly where there is potential for rapid vaccine development for multiple known or unknown pathogens. CEPI will also need to engage regulatory authorities - especially in vaccine producing countries – early in the development process so that these candidates may move seamlessly into efficacy trials in outbreak. CEPI will need to build and maintain platforms and networks to enable rapid trials and to expand access; to identify investors and define commitments in advance of needs for rapid scale-up of production and deployment of a vaccine during an outbreak. CEPI will develop plans or mechanisms for addressing unforeseen challenges that have direct implications for the success of CEPI's core mission. CEPI will consider liability responsibilities while advocating for sustainable liability plans that strengthen the confidence of fragile, epidemic-susceptible, countries. Finally, CEPI will plan surge capacity coordination mechanisms for financing large scale clinical testing and manufacturing during epidemics.

Strategic Objective 1: Preparedness

'Just In Case' Preparedness: advance late-stage EID vaccine development to enable full clinical testing and vaccination in the initial stages of an outbreak

CEPI will pursue advanced development (Phase I and II safety and immunogenicity studies) for priority pathogens. This will result in fast tracked execution of clinical trials to test efficacy (Phase III studies) in the initial stages of an outbreak, and potentially confer protection for at risk populations and healthcare workers at the epidemic frontlines.

CEPI's early programs will focus on candidate vaccines against two to three pathogens with the highest technical feasibility and likelihood of advancement through the R&D chain. CEPI will need to invest in more than one candidate per pathogen to account for attrition. A portfolio strategy and prioritization framework is therefore essential for the accurate planning and coordination of vaccine development efforts.

In order to advance EID vaccine development quickly, CEPI must also identify research, development, and manufacturing capacity obstacles and gaps. To accomplish this, CEPI will create and regularly update maps of vaccine development and manufacturing bottlenecks and capabilities worldwide.

In recognition of the important role of others already funding or coordinating R&D in this space, CEPI will selectively invest in those areas considered most important to meet its strategy while complementing others' resources or capabilities, as well as seeking to crowd-in financing partners across the end-to-end vaccine preparedness spectrum. Outlines of how investments and partnerships will be formed are laid out below in the sections *CEPI's partnership model* and *CEPI's investment process*.

EXPECTED OUTPUT 2021

- CEPI will have advanced four to six vaccine candidates against two to three priority EIDs to proof of concept and ready for Phase III, partnering with industry to ensure sufficient global vaccine development and manufacturing capacity.

ACTIVITIES 2017-2021

- Prioritize diseases against which vaccines will be developed
- Conduct gap analyses and assess vaccine pipelines for priority EIDs
- Design CEPI's vaccine development portfolio strategy and priorities in the EID space
- Implement CEPI's vaccine development portfolio strategy for two or three priority targets and deliver at least one Phase IIa/b vaccine candidate outcome per prioritized target
- Build dedicated partnerships with at least two vaccine manufacturing partners to leverage their capabilities for advanced vaccine development and manufacturing

Strategic Objective 2: R&D response speed

'Just in Time' Preparedness and R&D response speed: build technical and institutional platforms to accelerate research, development, manufacturing and clinical evaluation in an outbreak

CEPI will invest in technical and institutional platforms to accelerate R&D, manufacturing and evaluation in the event of an EID epidemic. CEPI will ensure these platforms are prepared to the fullest extent possible prior to an outbreak, by proactively working with key stakeholders to: invest in manufacturing platforms to accelerate development times; work with stakeholders including WHO to develop generic legal administrative measures to facilitate data sharing and collaboration that can be efficiently utilized in an emergency; work with developers and regulators to develop common protocols for adaptive randomized controlled trials; grow networks of outbreak clinicians that can respond in real-time; and establish MOUs with late stage development and manufacturing partners to provide surge capacity.

During an emergency CEPI will actively support and coordinate resources and activities across the spectrum of stakeholders in the rapid deployment of pre-emptive technical and institutional platforms for an outbreak. Outlines of how investments and partnerships will be formed are laid out below in the sections *CEPI's partnership model* and *CEPI's investment process*.

EXPECTED OUTPUT 2021

- CEPI will have established rapid response R&D capabilities and will have tested and refined these systems in the event of an epidemic.

Activities 2017 – 2021

- Set up new, or contract and sustain advanced development and manufacturing (ADM) facilities for pilot scale manufacturing and stockpiling of vaccines for Phase III testing in the event of an epidemic
- Plan in coordination with key stakeholders such as a GAVI rapid development and manufacturing in the event of an outbreak, including the delivery of stockpiled vaccines when applicable
- Utilize rapid vaccine discovery and development platforms where applicable and mobilize ADM facilities for scale-up manufacturing in the event of an epidemic
- Plan (and mobilize when needed) clinical trial centres in LMICs with protocols for Phase I, II and III trials in affected regions in strong partnership with the governments of those countries affected
- Plan (and deploy when needed) newly produced or stockpiled vaccines through necessary emergency use provisions
- Involve funders, vaccine developers, regulators and manufacturers, procurement and delivery agents in the planning and coordination of the above
- Establish tools, networks, systems and resources required in advance of an outbreak.

Strategic Objective 3: Market predictability

Secure industry participation through partnerships that share the risks and benefits of vaccine development

Industry engagement is a top priority for CEPI. The largest global vaccine manufacturers have demonstrated their commitment to the development of EID vaccines throughout the Ebola vaccine R&D response, but the direct cost to industry remains largely uncompensated. To a secure a robust partnership with industry, CEPI must establish a predictable and equitable system for sharing the risks and rewards of EID vaccine development to achieve CEPI's public health mission.

CEPI will develop or propose a number of industry incentives for application by national, regional or global jurisdictions outside its own domain of responsibility. Incentives should seek to reduce the cost, risk, and time for development; balance revenue with risk for losses and/or achieve other non-monetary benefits for CEPI and its partners. These incentive structures will be reasonably balanced to account for global access considerations under strategic objective 4.

EXPECTED OUTPUT 2021

- CEPI will have expanded the number and types of financing and incentive mechanisms directly supported or facilitated by CEPI, increasing global capabilities for EID vaccine development and manufacturing worldwide

Activities 2017 – 2021

- Research and scope incentives and business or partnership models that adequately reflect shared risk/benefit principles
- Establish standardized documents, contract templates and procedures that adequately reflect shared risk/benefit principles
- Develop incentives and business models (or propose incentives for others to endorse, at national or international level) to maintain industry participation. Examples include retaining of the propriety components or processes for commercial use e.g. through preferred tendering or stockpiling, regulatory exclusivity, patents, etc.
- Work with the WHO, regulators, governments and industry to reduce uncertainties around regulatory preparedness standards and protocols, ensuring optimal data sharing and agreements on clinical trial design in the event of an epidemic

Strategic Objective 4: Equity

Support the long-term development of regional capabilities for EID vaccine preparedness

CEPI will pursue collaborations with a number of stakeholders in regions where EID outbreaks are most likely to occur by forging partnerships with companies, governments, and other regional entities that have established capabilities for vaccine development, manufacturing and/or clinical testing. Such collaborations will boost support for CEPI's mission and expand the list of EID vaccine preparedness allies. CEPI must identify those entities across sectors with the highest capability building potential, and it should develop plans and procedures for technology transfers, clinical trial networks, and manufacturing surge capacity.

EXPECTED OUTPUT 2021

- Improved regional capabilities including in developing countries to support CEPI's core business model of advanced EID vaccine development and manufacturing, coordinated through partner networks in Asia, Africa and South America.

Activities 2017 – 2021

- Establish a node of the Secretariat at the Indian Department of Biotechnology with the role to work on international R&D and manufacturing capacity building within CEPI
- Map and utilize available capabilities for vaccine development and manufacturing across regions, with emphasis on regions where future outbreaks are likely to occur
- Map and utilize available clinical trial networks across regions where outbreaks of a priority pathogen are likely to occur
- Develop plans that facilitate access (through affordable prices and sufficient volumes) to EID vaccines for populations in need
- Collaborate with industry and government partners to develop technology transfer protocols and procedures for manufacturing if and only if relevant from the standpoint of decreasing cost per dose at same quality levels, when accelerating access to vaccines for larger populations is deemed to be a critical need (especially for rapid scale up manufacturing)

Cross-cutting: Ensuring success

Build integrated planning tools and sustain investments for end-to-end capabilities through joint coordination and management

We are setting up CEPI to sustain a level of preparedness for rapid technological innovation. This will require systematic planning and coordination for vaccine development, and reliable access to manufacturing capabilities. CEPI will develop an integrated system for planning and coordination, which will include: (1) product requirements setting tools and working groups that integrate industry and WHO perspectives; (2) a "tech watch" program to track opportunities for investment in vaccine candidates, research tools, and manufacturing processes that will accelerate development times; and (3) portfolio management tools, including models for pipeline / cost optimization and systems for grant management and reporting.

CEPI must also ensure an end-to-end approach to vaccine preparedness is in place, which will operate in coordination with other funders, regulators, manufacturers, procurement and delivery agents, and the WHO. Integrating and streamlining these activities will be a central component of CEPI's daily operational responsibilities.

The scope of this work will be predicated on the size of the initial investment. CEPI will work with its founding partners to support resource mobilization efforts through communications, advocacy, and policy. CEPI will need to build a diversified donor base to spread risk and ensure the long-term sustainability of its supported projects and organizations. The leveraging of CEPI's direct investments with co-investments in CEPI projects by other funders who may not be directly contributing into the CEPI funding pool will also reduce risk.

CEPI will conduct operations through a management structure that contains multiple Secretariat nodes with distributed capacities. Over the past year, CEPI stakeholders have begun to converge on a common understanding, strategic alignment and shared values. These values include transparency, reciprocal knowledge sharing, trust, and a set of common rules and norms.

EXPECTED OUTPUT 2021

- CEPI will operationalize a system for integrated portfolio planning and coordination of end-to-end capabilities, sustained funding and product development management. CEPI will ensure that key audiences internal and external to the coalition understand and support this system.

ACTIVITIES 2017 – 2021

- Develop integrated planning and coordination tools and working groups
  - Develop a project management framework, including Key Performance Indicators to assess current CEPI strategy and metrics for forecasting optimal portfolio targets for the future
  - Set up pathogen specific product requirements working groups in collaboration with the WHO and industry

    - Secure development of Preferred Product Characteristics (PPCs) / Target Product Profiles (TPPs) / requirements for the pathogens prioritized for CEPI funding
    - Develop and execute a “Tech Watch” program including the buildup and maintenance of a database on vaccine R&D pipelines and CMC/manufacturing capabilities
    - Design and execute pipeline / cost optimization tools to inform routine prioritization and strategic investment decision making
- Establish a Joint Coordination Group consisting of all formal partners of CEPI
- Develop and execute partnership strategies for knowledge sharing and quality relations between CEPI partners in alignment with CEPI objectives
- Develop and execute CEPI’s advocacy and resource mobilization campaign strategy with a focus on both global strategic partnerships and targeted regional relationships in emerging economies
- Identify and establish a permanent management team

Business framework

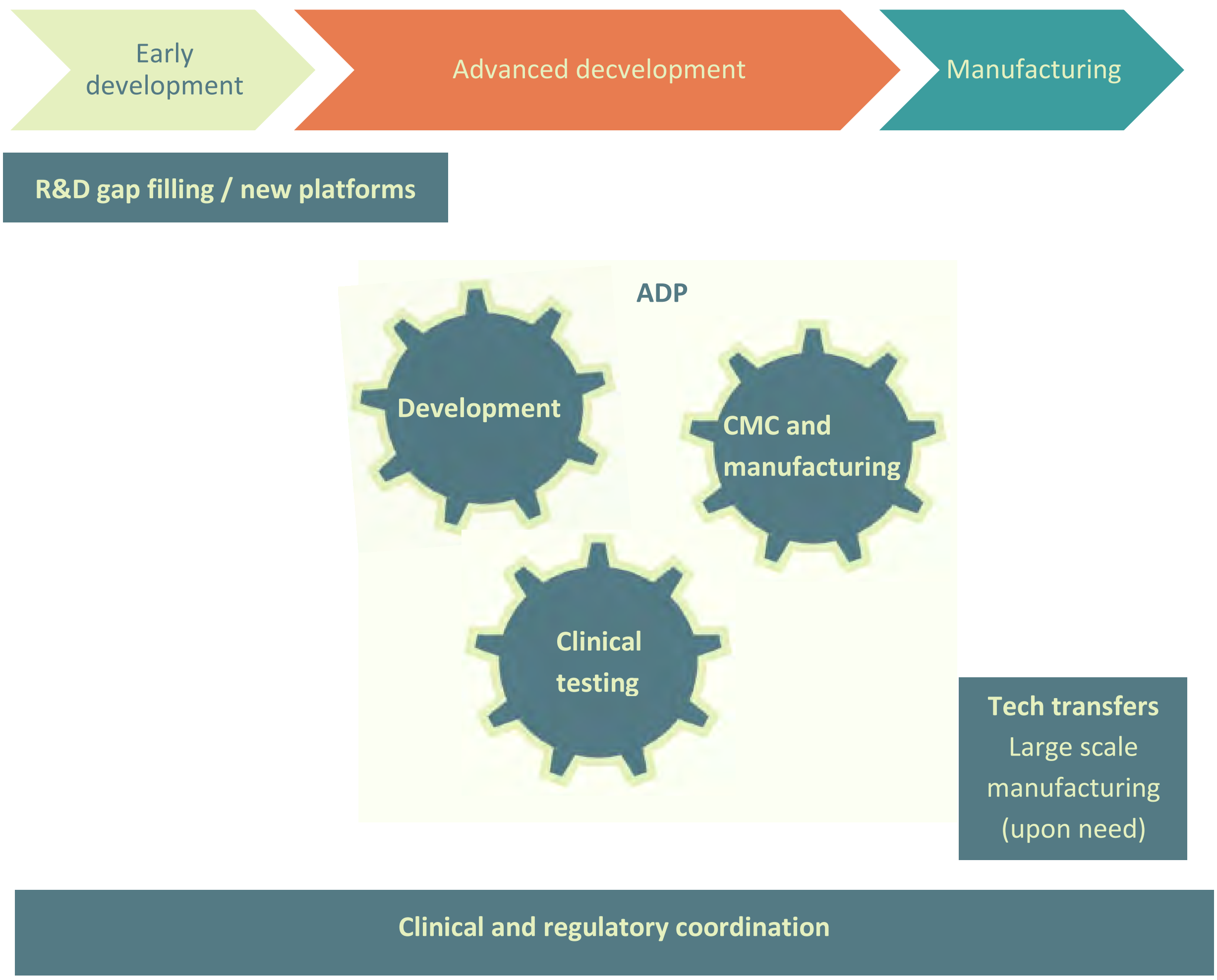
CEPI's partnership model

CEPI is building capabilities through a mix of partnership models.

At its core, CEPI includes an Advanced Development Partnership (ADP) consisting of a network of newly set up or existing and contracted ADM organizations to clinically develop vaccines against CEPI pathogens up to proof of concept and pilot scale manufacture.

Through joint coordination with others, CEPI will fill other R&D gaps at different stages of vaccine development as needed and will coordinate with other entities to set priorities, pathogen specific road maps and TPPs to manage stockpiling and distribution.

FIGURE 6: THE PARTNERSHIP MODEL



Advanced Development Partnership (ADP)

Priority is given to an ADP of dedicated and project-based capabilities. The ADP will research and develop vaccines from preclinical to a pre-determined clinical end point. The ADP will also develop, test, and maintain research tools and vaccine technology platforms that can rapidly respond to known and unknown EID threats. The ADP accommodates both permanently dedicated and project-based capabilities, providing a mixture of warm-base funding and project-based funding.[1]

Targeted investments for filling additional R&D gaps

Not all translational R&D gaps are likely to be filled by this advanced development partnership, and some pathogens will require a different set of capabilities that lie outside of the ADP. Project based funding mechanisms will allow CEPI to coordinate with a wider range of developers as needed. In some cases, funding for these projects will be 'outsourced' to other public programs or philanthropies. In this role, CEPI will promote synergistic efforts among product developers and funders across sectors and geographical regions.

Clinical and regulatory coordination network

Clear regulatory requirements, liability protection, and vaccine access guidelines are required to accelerate clinical testing and approval of products in epidemic situations. A network of the WHO, regulatory authorities (including mature and less experienced regulatory authorities) and industry will be set up to: (1) establish regulatory pathways for EID vaccines in epidemic situations; (2) develop model protocols and agreements for liability protection, data and sample sharing; and (3) identify, evaluate and prepare clinical trial centres and associated infrastructure in select, priority regions to enable large-scale clinical testing of vaccines in response to EID outbreak situations.

Complementary coordination initiatives

Coordination across the entire spectrum of vaccine preparedness and response is essential, even if CEPI's funding scope is limited to advanced development and small-scale manufacturing. This includes coordination with other funders, regulators, R&D implementers, vaccine procurement, stockpiling and delivery agents and normative agencies such as the WHO that set priorities and develop pathogen-specific road maps and TPPs. Coordination is key with entities having primary responsibility for response, e.g. WHO, UNICEF and GAVI. Such links will enable rapid response, spanning from the ability to scale up manufacturing to involving LMIC manufacturers in the long term.

[1] A warm base refers to facilities that would be operationally ready to quickly develop and manufacture vaccine during an epidemic, as well as maintain capacity to provide core services to CEPI for the development of vaccines in off-epidemic situations.

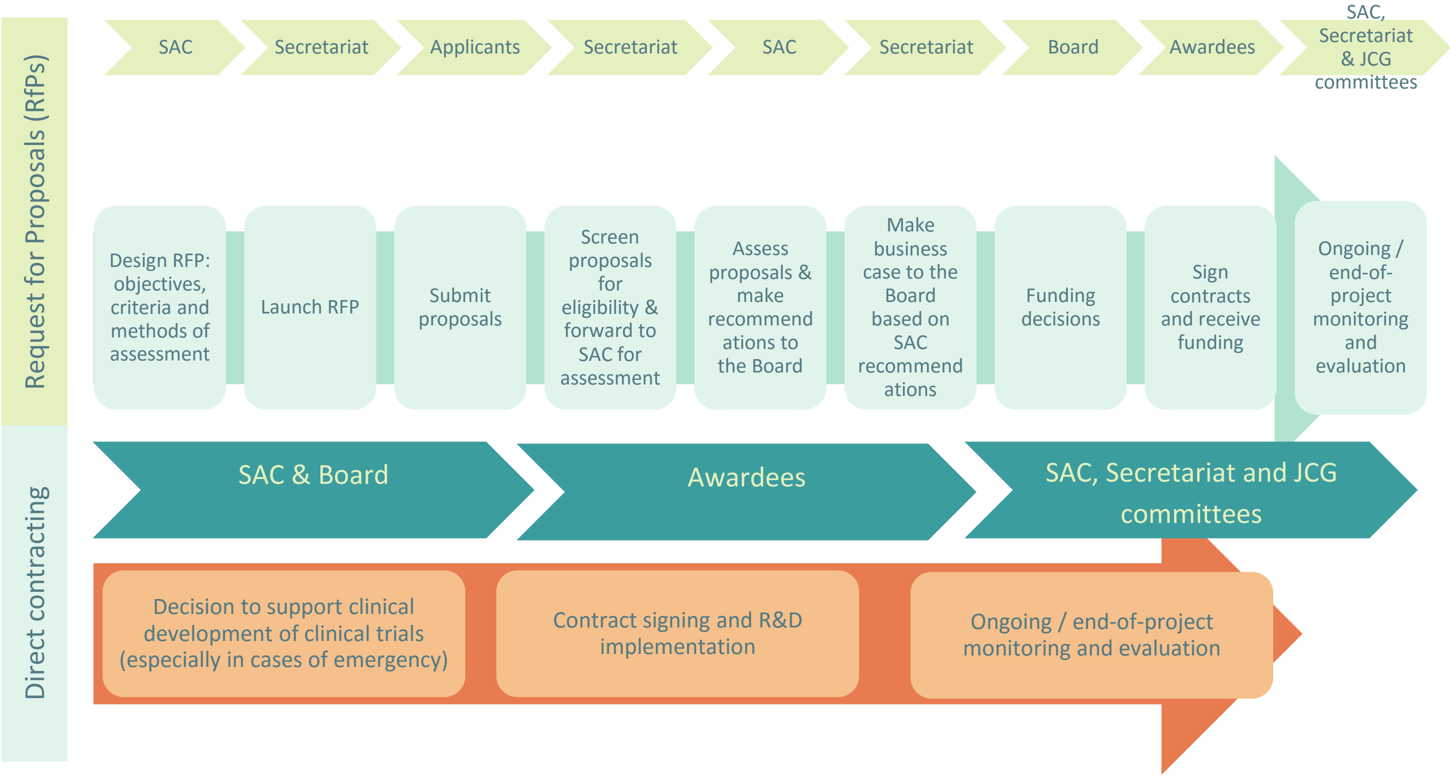
CEPI's investment process

CEPI invests through Requests for Proposals (RFPs) and through direct contracting, based on technical recommendations by the SAC and decisions for funding by the Board.

In most cases investments will be executed through requests for proposals (RFPs). CEPI's Scientific Advisory Committee (SAC) has the supreme advisory role in the design of RFP technical content, including criteria and methods for assessment of applicants for CEPI funding. RFPs can range from broad announcements made in the public domain (e.g. CEPI's website) to restricted announcements targeted to organizations with known capabilities. Secretariat staff will screen proposals for eligibility and forward proposals for assessment to the SAC. Eligibility criteria and methods for proposal assessments will be specified in respective RFPs, according to SAC directions. The SAC will undertake full proposal reviews and provides recommendations for funding to the Board. The Board will make final decisions for funding. The investment process will conclude with contract signing and R&D implementation. Monitoring and evaluation will be ongoing and will include an end-of-project cycle review with decisions on termination or continuation of the investment.

In exceptional circumstances – e.g. in emergency situations - CEPI investments will be executed through direct contracting, requiring rapid assessments and decisions to support vaccine development or clinical testing. Over time, CEPI may diversify its tools for channelling investments to include proactive scanning and soliciting relevant projects under the SAC's scientific oversight and overall technical direction.

FIGURE 7: CEPI'S INVESTMENT PROCESS



CEPI's operating principles

Three operating principles serve as the foundation of CEPI's strategic and business framework:

Equitable access	Global access arrangements will be negotiated in contracts between CEPI and vaccine developers to ensure affordability and availability in Low and Middle Income Countries (LMICs). The price of vaccines developed through CEPI should not be a barrier to access.
Cost coverage	Vaccine developers who contribute with dedicated capacities should be reimbursed for their direct and indirect costs.
Shared benefits	It is anticipated that vaccines developed with CEPI support will not be profitable. In the event that a CEPI-supported vaccine becomes profitable, agreements between CEPI and the developer will ensure either that CEPI's investment is reimbursed or that profits are shared through royalties or other mechanisms. Any rewards that accrue to vaccine developers should be proportionate to the level of risk undertaken and the contributions (R&D, infrastructure, IP) a developer has made.

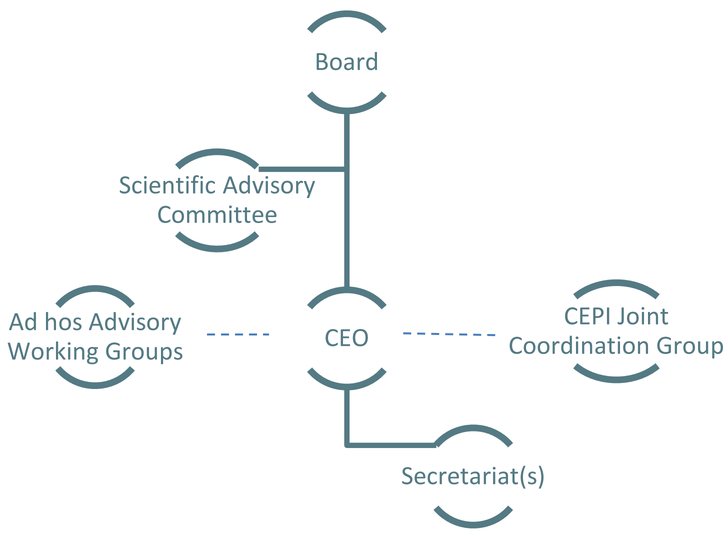
Organization and governance: startup phase

The CEPI Board governs CEPI and a CEO-led management team coordinates the day-to-day operations of CEPI through a core secretariat node in Norway and nodes with distributed capacities worldwide. A Scientific Advisory Committee advises CEPI on scientific matters and a Joint Coordination Group coordinates CEPI's activities with other actors across the spectrum of vaccine preparedness and R&D response planning.

Organizational structure

CEPI's organizational oversight (see Figure 6) includes governance, management and coordination, and advisory functions. The two permanent institutional bodies of CEPI established under its Articles of Associations are the CEPI Board, and the CEPI Secretariat. Two other organizational structures are established to fulfil advisory and coordination functions: the CEPI Scientific Advisory Committee (SAC) and the CEPI Joint Coordination Group (JCG). Optionally, the CEPI Board may establish other committees or advisory working groups to address specific issues. An advocacy structure will be established in the form of a more loosely defined group of CEPI champions, serving as a group of ambassadors and advocates for CEPI's mission.

FIGURE 8: CEPI GOVERNANCE ARRANGEMENTS



Interim arrangements for the startup phase

During the interim period, CEPI's Secretariat will be hosted by the Norwegian Institute of Public Health (NIPH) under a service agreement defining the terms and conditions. NIPH is Norway's primary public health institute under the Norwegian Ministry of Health and Care Services, providing scientific public health advice to governmental authorities, the health service, and the general public. The NIPH is responsible for procuring all vaccines for the Norwegian health system. This necessitates sufficient level of institutional independence from CEPI, given CEPI's close collaboration with major vaccine manufacturers. It is also of importance to protect CEPI from undue influence from the host organization. For the interim period, both objectives are deemed to be best fulfilled by the establishment CEPI as an independent legal entity as an international non-profit association organized under Norwegian law. The founders of the association are the Gates Foundation, the World Economic Forum, the Wellcome Trust, India's Department of Biotechnology, and the Government of Norway.

Governance

CEPI Board

The CEPI Board (the Board) is the highest decision making body of CEPI, and has supreme decision-making authority for all funding, policy, and product development aspects of CEPI's operations. During the interim period the Board will:

- Provide governance and fiduciary oversight
- Ensure that the organization is managed effectively by the CEO and the CEPI Secretariat, in accordance with legal and regulatory requirements
- Define directions and policies for pursuing the organization's mission, and ensure the organization follows plans and budgets that are in line with it
- Approve plans, programmes, budgets, fundraising strategies, and operational policies (including a conflict of interest policy, risk management framework, and scales of staff salaries and benefits)
- Perform tasks and functions necessary for the attainment of the organization's mission, including the delegation of any of its powers or decision-making authority to the CEO, and the establishment of working groups and committees as it deems necessary for the performance of its functions
- Set the conditions under which any tranche of CEPI funds will be released
- Oversee the establishment of the permanent CEPI Board
- Appoint the permanent CEO
- Authorize the CEO to execute on decisions not falling under his/her delegation of authorities
- Consider such other matters related to CEPI as may be referred to it by the CEO.

The composition of the CEPI Board reflects the main stakeholders committed to fulfilling CEPI's mission. The Interim Board is composed of: (1) 3-5 HIC government representatives; (2) 3-5 LMIC government representatives; (3) 2-3 philanthropic funder representatives; (4) 3-4 private sector representatives, of which 2 will constitute MNCs who have signed a Memorandum of Understanding with CEPI; (5) 1-2 representatives from civil society/NGOs/patient organizations; (6) 1-3 members in their individual capacity. Subcommittees and constituencies can also be established at their discretion, including a funders group across HIC, philanthropic and LMIC organizations.

A number of organizations participate in the Board as observers (with the right to speak, but not to vote): (1) WHO; (2) Chair of the CEPI Scientific Advisory Committee; (3) Chair of CEPI Joint Coordination Group and (4) CEPI CEO.

Management & Coordination

CEO and Secretariat

The Interim CEO is responsible for executing the decisions made by the Board, providing operational management and executive authority for all funding, policy, and product development aspects of CEPI operations. The interim CEO serves as the legal representative of the organization, and is empowered as decided by the Board to sign deeds, contracts, agreements and other legal documents necessary for the organization's operations, within the limits of Delegation of Authority policy approved by the Board.

The CEO is supported by a Secretariat structure with:

- core support services: executive leadership support; finance; IT, administration & human resources (could be provided as a service by a larger host organization); external relations; policy relations; business development; legal; fundraising, advocacy and communication support.
- vaccine development coordination: technical support and administration of CEPI's vaccine development operations, including joint oversight of vaccine development activities implemented by CEPI beneficiaries and consultations with the Scientific Advisory Committee as appropriate.
- clinical & regulatory coordination: optimization of collaborations and partnerships for an enabling regulatory environment across the vaccine ecosystem; support of task forces or committees appointed by the CEPI Joint Coordination Group to generate clinical trial designs and regulatory science innovations; seeking of sustainable and mutually beneficial solutions to liability protection; identification and capitalization of suitable clinical trial infrastructures in close proximity to areas with high EID outbreak potential.
- portfolio management, monitoring & evaluation: ongoing assessment of CEPI's portfolio against CEPI strategy, objectives and KPIs; the selection and oversight of the work of auditors assessing CEPI's implementation of R&D policies, resource allocations, operations and management and overall compliance to CEPI's statutory provisions and standards.

The secretariat operates through a core node in Norway and other nodes in committed partner organizations around the world. The permanent structure and location of the secretariat is to be decided through an open process. In the meantime and under direction of the Interim CEO, the Interim Secretariat will:

- establish management procedures, including developing a business plan for approval from the CEPI Board;
- recruit the necessary staff to fulfil the functions of the Interim Secretariat, including core executive leadership support services, coordination of vaccine development and clinical & regulatory affairs, monitoring & evaluation services;
- develop consolidated work plans, including plans and budgets for the Interim CEPI Secretariat;
- develop the necessary operational guidelines to be approved by the Interim Board;
- provide project management and monitor progress of activities against CEPI milestones;

- develop reports on finance including costing and funding requirements;
- coordinate resource mobilization strategies;
- provide the administrative support to the Interim CEPI Board, the Interim Scientific Advisory Committee, and the Joint Coordination Group;
- conduct activities to meet communication, advocacy and fund raising needs;
- disseminate information relating to CEPI;
- provide additional services as required

Advisory & Coordination

Scientific Advisory Committee

The CEPI Scientific Advisory Committee (SAC) is the principal advisory group to the Board and the CEPI Secretariat on scientific matters important to the operations of CEPI. This includes, but not limited to:

- Recommending priority pathogens for consideration of CEPI focus and support.
- Develop descriptions for Request for Proposals (RfPs).
- Reviewing proposals submitted in response to RfPs for vaccine research and development programs targeting priority pathogens.
- Recommending to the Board funding of proposals aiming to move vaccine candidates for priority pathogens from the preclinical stage to proof-of-concept demonstration in humans.
- Recommending the continuation or cessation funding of CEPI-supported research efforts at the end of defined program milestones for CEPI-supported vaccine development programs.
- Monitoring progress of CEPI's overall vaccine portfolio, and reviewing the overall quality of progress of CEPI's scientific operations.
- Updating the CEPI Board on important new research developments in science and technology relevant to achieving CEPI's mission.
- Providing scientific input, as requested by the CEPI Board, to inform their efforts to advance solutions for overcoming obstacles to successful and expedited end to end development and delivery efforts for vaccines targeting CEPI-prioritized pathogens

The Board may decide to seek advice from the SAC for other scientific matters relevant to the operations of CEPI. Final decision-making about the issues addressed by the advice and recommendations from the SAC rests with the Board or the CEO. The SAC has no executive function in the operations of CEPI. The CEPI Secretariat facilitates the work of the SAC. The SAC acts independently of all the governing structures of CEPI, including the CEPI Board, the CEO and the CEPI Secretariat, the CEPI Joint Coordinating Group, and the CEPI Champions.

The advisory committee is composed of a group of 23 qualified individuals, representing core areas of scientific expertise needed to advise the Board. In addition there is one observer from the WHO, with the right to express views but not to vote. There are also 3-4 industry experts to the SAC as non-voting members (i.e. observers), who are not representatives of individual companies but nominees of the constituency of multinational biopharmaceutical companies in CEPI. The combined expertise of the advisory committee reflects the end-to-end spectrum of vaccine development, covering the following areas of core scientific expertise: (1) Public health significance of new and re-emerging infectious diseases of epidemic potential, including infectious disease epidemiology, infectious disease modelling and biostatistics; (2) Vaccine R&D, including biochemical engineering, vaccine immunology, vaccine adjuvants and vaccine delivery

systems, bio-banking and sample sharing, early phase vaccine development, including expertise on preclinical and animal models, and clinical assays; (3) Vaccine manufacturing, including vaccine formulation, manufacturing platform technologies, good manufacturing practices (GMP), quality control and quality assurance, scale up bulk manufacturing, stockpiling and distribution; (4) Vaccine licensure, including regulatory affairs and CMC requirements for global vaccines, IP management, vaccine safety, vaccine risk/benefit assessment and bioethics; (5) Vaccine implementation, including vaccine procurement and vaccine deployment during epidemic outbreaks.

The members of the advisory committee serve in their personal capacity as independent experts, and refrain from promoting views and policies of the institution for which they work. Members of the advisory committee are appointed to serve for an initial term of two years. This two-year term may be renewed once, but to facilitate diversity of expertise, the term is only renewed for maximum 2/3 of the membership at the same time. To allow for continuity in the operations of the advisory committee, there is an option for the Chair to renew his or her term (such option to be triggered at the CEPI Board's discretion), but only once. The Chair can act for a maximum of four years. The Board reviews bi-annually the composition of the SAC, and may actively seek to attract nominations reflecting other needed areas of expertise. Prior to being considered for membership, nominees are required to complete a Declaration of Interests form. An updated Declaration of Interests form must be submitted for review to the CEPI Board 14 days prior to each Scientific Advisory Committee meeting. Potential conflict of interests are managed in accordance with CEPI's Conflict of Interest Policy.

The main criteria guiding selection of members are technical expertise in line with the categories above, diversity of stakeholders (academia, governmental agencies, private sector and civil society/NGOs/patient organizations), geographic representation, and gender balance. Securing the technical competencies and the diversity of stakeholders reflecting the end-to-end of vaccine development and application is given priority when selecting members. Geographic representation and gender balance is given due consideration, including securing representativeness from hot spots for emerging and re-emerging infectious diseases.

Joint Coordination Group

The different programmatic priorities of the various coalition partners of CEPI necessitate a mechanism by which the CEPI coalition partners align among themselves, and coordinate their own activities across the end-to-end spectrum of vaccine development for priority pathogens. To fulfil this function, a Joint Coordination Group (JCG) has been established for CEPI partners to share information, promote alignment and encourage coordinate their efforts to secure efficient use of resources for R&D of vaccine candidates against priority pathogens that lack market potential.

The JCG promotes coordination and supports efforts for the alignment of funding, R&D implementation, regulatory processes, procurement and stockpiling actions between CEPI partners positioned at different levels of the end-to-end vaccine preparedness spectrum for priority pathogens. It aims to optimize response planning related to large scale clinical efficacy testing during public health emergencies, scale up manufacturing, regulatory approval and large scale procurement of EID vaccines upon need and beyond the day-to-day scope of CEPI operations. In addition to serving a coordination function, the JCG serves a joint advisory

function to the Board, and facilitates the involvement of CEPI partners for the strategic direction and policy oversight for CEPI's operations.

The JCG will be represented by partners who have signed a Memorandum of Understanding committing to contributing to fulfil the CEPI's mission. In principle, three types of coalition partners will exist:

- Funders: commit tangible assets and delegate the decision-making authority for the use of these assets to the Board.
- Co-funders: commit financial resources or infrastructure to vaccine development through their own mechanisms.
- Facilitators: This third type of partner does not commit tangible assets, but commits to CEPI's mission by addressing other critical areas of end-to-end vaccine development. These may concern normative guidance on data sharing and clinical trial design during emergency response, or accelerated regulatory assessment and approval pathways. Examples of partners here include R&D implementers (e.g. MNCs, research institutes, PDP), regulators and normative bodies (e.g. US FDA, EMA, WHO PQ, AVAREF), procurers and distributors at the global level (e.g. Gavi).

Each member of the JCG is entitled to appoint one representative to the JCG. Each member of the JCG is expected to express the views and policies of the institution(s) they represent.

The composition of the JCG during the interim phase will consist of: The WHO; CEPI (represented by CEPI's CEO; CEPI's Chair of the SAC); core funders (e.g. Wellcome Trust, Gates Foundation, Norway) and co-funders (e.g., BARDA, EC, IMI, and NIH); public and private sector implementers/innovators (e.g. MNCs, research institutes, PDPs); regulators and normative bodies (e.g. US FDA, EMA, WHO PQ, AVAREF, national academies of medicine or science), procurement and distribution partners (e.g. Gavi). An independent Chair of the JCG is appointed by the Board.

Other committees and advisory working groups

The Board may establish other committees or advisory working groups to address specific issues, depending on need and after some time from CEPI's inception:

- Joint Steering Committees (JSCs) may be established to oversee programs or projects co-funded with others. JSCs may be delegated the oversight of such programs and projects, reporting to the CEPI CEO. CEPI Secretariat staff or individuals appointed by the CEPI Secretariat will compose these, as well as representatives from other co-funding organizations, and potentially representatives from the implementing organization.
- *Ad hoc* Advisory Working Groups may be established to inform the CEPI Board, the CEO, SAC and JCG with evidence-based recommendations on various issues across the end-to-end spectrum of CEPI's operations, but with no binding commitment for decision making.

CEPI Champions

A CEPI Champions group serves as an advocacy platform; comprising a group of ambassadors of and champions for CEPI's mission, contributing to the mobilization of political and financial capital. Members include political champions, advocacy leaders in fields relevant to CEPI's mission, representatives from countries, public and private sector organizations with strategic

interest in vaccine development. Key functions include: (1) to manage perceptions / advocate for vaccines and policy change at global and local level; (2) to promote achievements and communicate results to global, regional and local audiences; (3) to link with other fora, groups and platforms for public dialogue and collaboration among stakeholders in the EID preparedness field; (4) to fundraise.

Organizational principles

Legitimate and effective governance arrangements are essential. This requires a number of organizational principles to be in place: Accountability; Public trust; Political legitimacy; No conflict-of-interest; Transparency; Independence / Neutrality; Public interest representation; Flexibility / Nimbleness; Global health responsibility. The CEPI Secretariat is developing policies and procedures to operationalize these principles. These will be finalized by the end of CEPI's interim period of operation and include:

- Conflict of Interest (COI) policy and a Register of Conflicts;
- Dispute Resolution policy and procedures;
- Financial Framework, including an audit policy, procedures for maintaining financial records and evaluating the financial health of CEPI;
- Funding policy including: ratio thresholds between sectors and caps in shares of total funding by single entities, to ensure independence of CEPI strategy development over time; ratio thresholds between sustainment and project-based funding to allow for flexibility of funding upon need;
- Salary policy, earmarking wages to standard market equivalents in the respective countries where CEPI staff operates by profession;
- HR policy;
- Access policy according to which: target product profiles reflect normative directions; provided by the WHO, technical requirements proposed by the CEPI advisory working groups and are publicly available; terms of reference agreed early on with industry partners for reasonable vaccine development costs and vaccine pricing;
- IP and licensing policy that focuses on CEPI's mission, and which revolves around principles of non-exclusivity, non-rivalry, and where possible, transferability and open innovation principles;
- Stringent Procurement policy and standard operating procedures to select and retain providers for required activities ensuring efficiency and quality of services over time;
- A risk/reward sharing policy, whereby a mechanism will be put in place to recoup a fair and reasonable return in the event that a CEPI funded product becomes very profitable for a private entity;
- Risk Management framework;
- CEO Delegation of Authority policy, clarifying the decisions the CEO can make only when formally authorized by the Board
- Other policies as deemed necessary and / or appropriate

Investments

CEPI should invest USD 1 billion today in order to advance four to six vaccine candidates to proof of concept in five years, based on currently known vaccine pipeline- related and expected CEPI budget- related constraints and a portfolio target of two to three WHO R&D Blueprint listed pathogens for this time period.

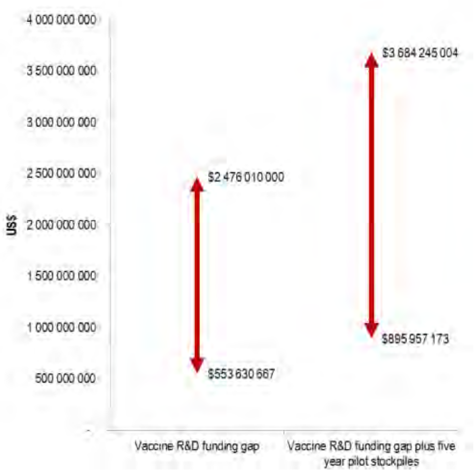
Measuring the funding gap

Estimates to advance pipelines with active vaccine candidates for 10 WHO R&D Blueprint pathogens[2] to proof of concept within five years vary depending on the complexity of the vaccine technology, pilot plant requirements, and other manufacturing cost variants.

Vaccine development efforts starting today can cost at least USD 0.6 billion over five years. This figure assumes that at least one and not more than three vaccine candidates must be advanced to ensure four successful phase 2a outcomes across 10 diseases in five years. If one is to consider the most innovative or complex technologies for the development of these vaccines (which may well be the case for many of these pathogens), total costs may add up to USD 2.5 billion in total).

Vaccine development efforts starting today with pilot manufacturing and stockpiles for Phase III testing in the event of an epidemic can cost at least USD 0.9 billion over five years, if again at least one and not more than three vaccine candidates were to successfully reach end of Phase II testing against the 10 WHO R&D Blueprint pathogens by the end of this time period. This figure also considers the total costs of setup of one to two pilot manufacturing plants and their usage as well as generally pilot stockpiling and maintenance for a five year period after vaccine candidates have reached end of Phase II testing, total costs. These costs can rise up to a total of USD 3.7 billion, if the most advanced technology platforms and cutting edge manufacturing capabilities are deployed.

FIGURE 9: GLOBAL FUNDING GAP FOR VACCINE DEVELOPMENT AND PILOT STOCKPILES IF 1-3 PHASE II VACCINE OUTCOMES WERE TO BE ACHIEVED PER PATHOGEN IN FIVE YEARS, FOR 10 WHO R&D BLUEPRINT PATHOGENS

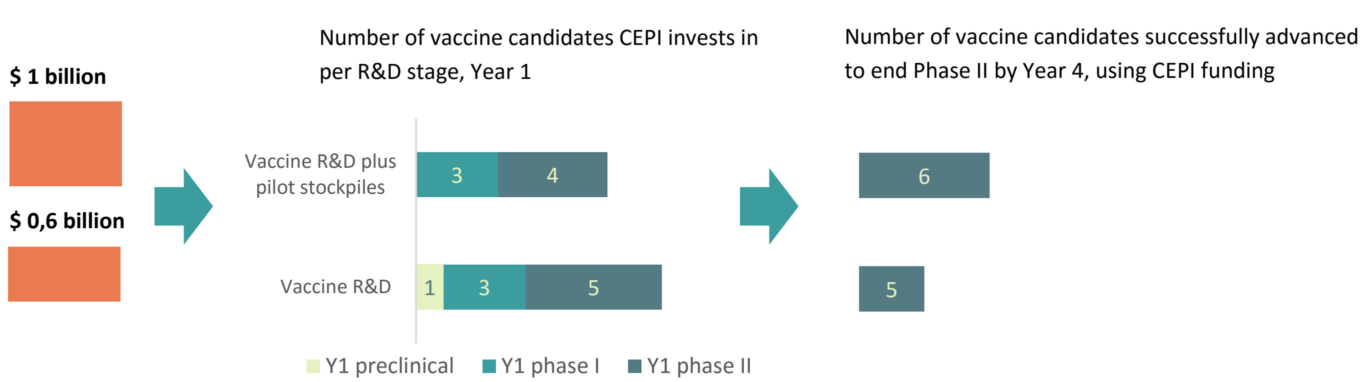


[2] This WHO number excludes SFTS, which does not have any projects in the pipeline.

Closing the funding gap

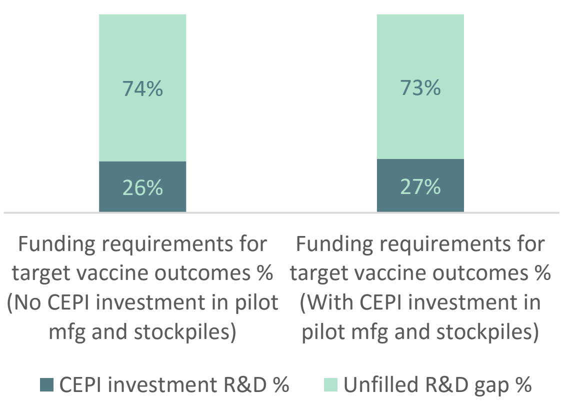
Based on a deterministic optimization model, CEPI estimates that the maximum cost range for vaccine development in the first five years is between USD 0.6 billion (only for vaccine development up to Phase II) and 1 billion (if pilot scale manufacturing and maintenance of five year pilot stockpiles are included). This cost estimate is based on the assumption that CEPI aims for at least four and not more than six vaccine candidates successfully advancing to end of Phase II at the end of the five year period, corresponding to at least two and maximum three prioritized pathogens. Given attrition rates, CEPI would need to invest today in seven to nine vaccine candidates at different stages of preclinical or early clinical development (see figure 10):

FIGURE 10: EXPECTED NUMBER OF VACCINE CANDIDATES CEPI FUNDS IN YEAR 1 IN ORDER FOR 4 - 6 OF THEM SUCCESSFULLY REACHING PROOF OF CONCEPT IN YEAR 5



Based on currently known (e.g. current vaccine pipeline structures for the WHO R&D Blueprint pathogens) and expected resource constraints (e.g. an assumed CEPI budget need of USD 1 – 2 billion made by the Task Teams), and a CEPI portfolio strategy of two to three prioritized pathogens with four to six vaccine candidates advanced successfully to end of Phase II over five years in total, CEPI is filling over a quarter of the global funding gap in this space through investments of up to USD 1 billion.

FIGURE 11: CEPI CONTRIBUTIONS IN FILLING THE GLOBAL FUNDING GAP FOR VACCINE DEVELOPMENT AND PILOT STOCKPILES AGAINST 10 WHO R&D BLUEPRINT PATHOGENS



It is likely that a significant part of this funding gap is already covered by national, supra-national and philanthropic funders in select high income countries (e.g. USA, UK, France, EC / IMI), matched by in kind contributions and commitments from vaccine manufacturers engaged in such supported R&D ventures. In addition, the gap could potentially be smaller if one assumes that only two Phase II vaccine candidates would be sufficient for at least one of them to advance through Phase III testing and licensure successfully in the event of an epidemic, accounting for risk of failure. This is a plausible assumption in the case of EIDs, where risk of failure at Phase III testing may be smaller if sufficient flexibility and speed is demonstrated around clinical trial designs and regulatory pathways.

TEXTBOX 4: Sources and assumptions on cost data

Cost inputs (see table 2) are based on figures provided by CEPI's Task Team 1, Subgroup 3, from their own analyses during and prior to CEPI's inception. The range of cost inputs is wide due to a multiplicity of factors including:

- differences in R&D costs depending on the complexity of the vaccine technology used
- differences in manufacturing setup costs depending on whether Contract Manufacturing Organizations (CMOs) are used or whether new pilot plants are set up
- differences in manufacturing usage and stockpile costs depending on the manufacturing platform used

TABLE 2: INPUT PARAMETERS

	Preclinical	Phase I	Phase II
1. Development times per R&D stage (years)	1,5	2	1,5
2. Unit costs per R&D stage			
Lower bound	*16.7m*	*7.5m*	*10m*
Upper bound	*66.7m*	*18.8m*	*66.7m*
3. Success rate per R&D stage	57 %	72 %	79 %
4. Manufacturing setup costs			
Lower bound (no setup, only CMOs)	-		
Upper bound (1 to 2 new pilot plants)	50m		
5. Manufacturing usage / CMC costs			
Lower bound (recombinant viral vector)		*0.8m*	*0.8m*
Upper bound (live or killed virus)		*23.2m*	*23.2m*
6. Stockpile maintenance (annual)			
Lower bound			*5m*
Upper bound			*10m*

Other assumptions include:

- Cost figures are assumed to be valid for late preclinical, Phase I, and Phase IIa only
- The model assumes different entry points for different vaccine candidates in the analysis, depending on the current structure of the pipelines per pathogen included
- All projects identified in the pipelines are assumed to be at the start of their respective stages of development
- It is assumed to take 5 years for a successful candidate to advance from late preclinical to end of Phase IIa
- No outbreaks occur in the five years, which would necessitate Phase IIb or Phase III trials, scale up manufacturing and other regulatory or delivery costs.
- Resources are not diverted to Health Emergency response for a pathogen not currently contained on the WHO list of Severe Epidemic Threats.
- In terms of technical feasibility, the same average success rate per R&D stage applies to all pathogens.
- Figures include industry average direct and indirect costs, but no cost of capital / opportunity costs. No estimates are included either for: regulatory costs, basic research and discovery costs, advanced Phase II or Phase III costs and delivery costs.
- Model is agnostic as to TPPs / PPCs / product requirements.
- Model is agnostic as to pathogen-specific vaccine development plans and assumes types and numbers of animal or clinical studies per R&D stage at the lower end of cost estimates
- Model assumes a single, strategic investment decision for the five years taken in Year 1
- Model is agnostic as to warm-base requirements or manufacturing capacities to support pilot mfg/stockpiles
- Model is agnostic as to geographical location of vaccine development, clinical testing or pilot manufacturing

Resource requirements for CEPI management and coordination

CEPI needs human and infrastructural resources for coordination to meet its five year strategic objectives.

- Human resources: minimum number of staff and consultants to support the management structure requires around 15-20 staff across the Secretariat nodes.
- Infrastructural resources: office space, equipment, consumables, IT, legal and other administration support services.

Assuming a management structure whereby the Secretariat nodes are hosted in already existing organizations with minimal infrastructural setup requirements, annual costs range from USD 4 – 5 million, depending on overhead charges of hosting organizations. Different estimates would be required in the case of other management structures.

Financing

CEPI needs to raise USD 0.6 – 1 billion to support a five year portfolio strategy of two to three prioritized pathogens and two to three Phase IIa/b vaccine candidate targets per prioritized pathogen by the end of this period.

Financing principles

CEPI will source and use financing to achieve its mission revolving around four key financing principles:

- **Broad-based financing**: secure support from the broadest possible base of funders, spreading funding risk and broadening the potential donor base for accelerated R&D in the event of an epidemic
- **Long term, predictable financing**: by focusing on later stages of vaccine development, CEPI can define objectives with a certain degree of granularity, justifying requests for long term financing from donors due to lower funder risk. Certainty of financing over a longer time horizon also incentivizes industry to commit assets and knowhow to CEPI efforts.
- **Complementary and new financing**: a core pillar of CEPI's financing strategy is to complement rather than crowd out existing funding. Therefore CEPI should seek and capitalize wherever possible opportunities for appropriate parallel funding for programmes of others e.g. BARDA, IMI or national R&D programmes worldwide.
- **Fit-for-purpose financing**: Financing mechanisms must be flexible and suitable to variable degrees of risk/reward needs. This requires CEPI to set up resource mobilization mechanisms that can be tailored to different sectors or geographies and which can adequately reward ability to stimulate innovations as well as create public health impact.

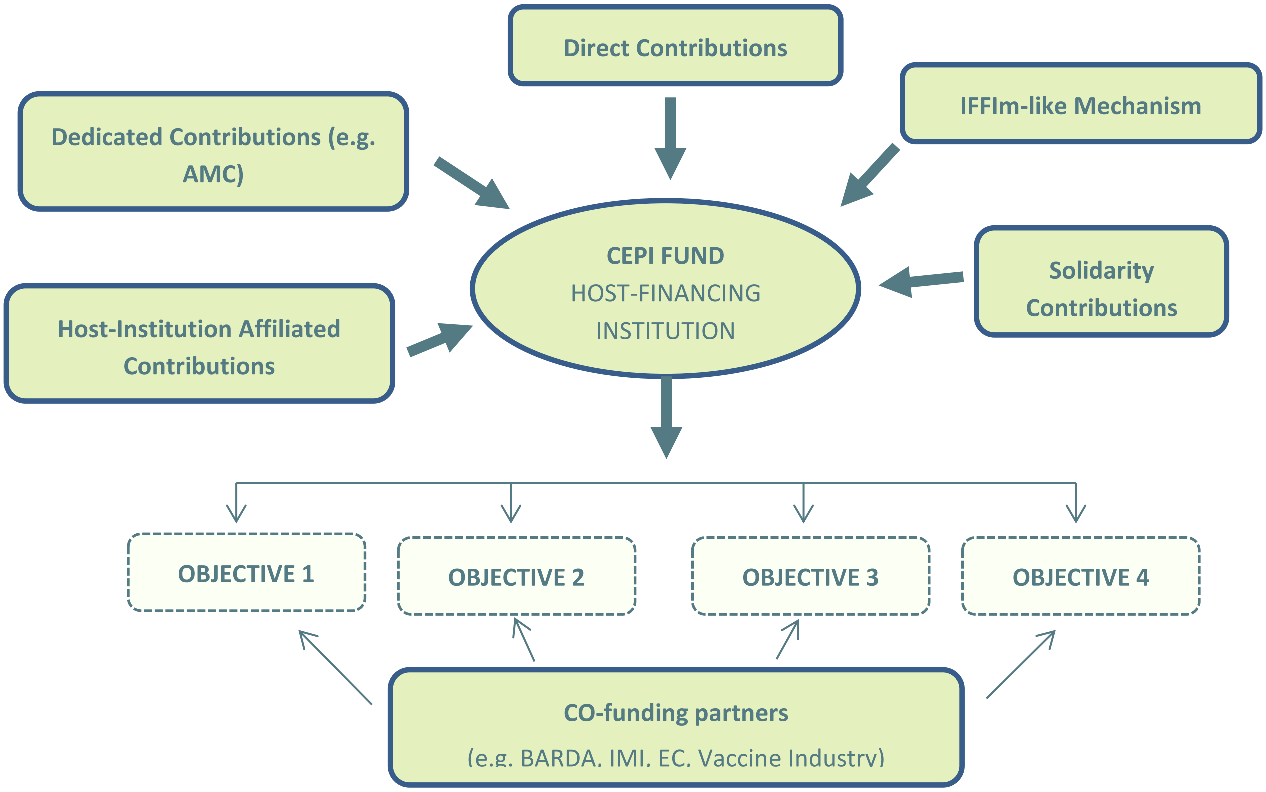
Sources of financing

CEPI seeks multi-year donor commitments to satisfy its core financing needs, as well as target investments directed specifically to CEPI priority targets.

There is broad agreement among CEPI partners that long-term and predictable financial commitments are required, ideally with 10 year time horizons. However, this objective will not be fully realized until CEPI has a demonstrated ability to deliver on its promises. The first five years of CEPI operations are a reasonable time horizon for testing how CEPI can add value to the field. It is foreseen that no single model will perfectly fit every potential funder, and a multi-source fundraising strategy is essential. Where donors cannot make multi-year investments, CEPI will spread upfront capital raised by some funders with capital raised as appropriate in subsequent years through multiple sources. Where innovative financing mechanisms can be used to generate multi-year cash flows, these will be encouraged. Figure 12 presents how direct contributions (core multi-year pledges or targeted investments) and blended capital sources could collectively comprise the core source of CEPI financing during its first years of operation. An International Finance Facility for Immunisation (IFFim)-like mechanism and solidarity contributions are considered especially relevant, but other sources of financing could also be

considered by the Board, depending on need and evidence based recommendations by expert groups.

FIGURE 12: A MULTI-SOURCE FINANCING MODEL



CEPI's funding mix between sources (e.g. multi-year core donor commitments vs earmarked investments targeted at specific CEPI priority targets) and between years of operation will depend on the level of financing primarily by its Founding Partners, other major governments and donors.

CEPI will develop a fundraising strategy in which it will seek diversified sources of financing whilst respecting the four core financing principles outlined above (see Table 3). Overall, priority will be given to direct cash contributions to a CEPI pool. Blended capital options will be considered as tools to generate additional financing.

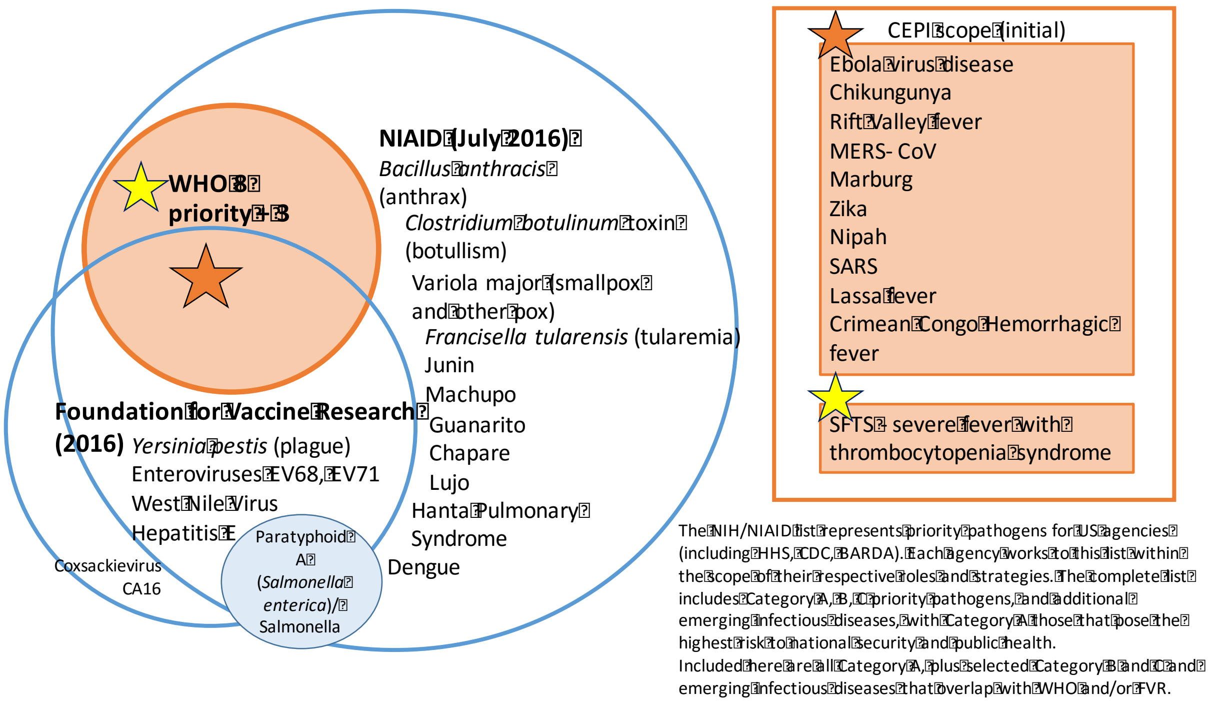
TABLE 3: RESOURCE MOBILIZATION MECHANISM EXAMPLES

Source	Mechanisms	Indicative examples of real-time application
Governments / citizens / philanthropists	Government budgets, taxes and fees, voluntary consumer-based contributions, buy-downs, lotteries, private giving campaigns, pooled funding	- ODA and national health R&D budgets - Earmarked taxes and fees / e.g. airline ticket tax - Various consumer voluntary contributions - Private giving campaigns - Pooled funding - Pledge / guarantee backed debt/equity financing
Private sector	retained earnings, pooled funding, donations, in-kind contributions, debt/equity instruments	- Retained earnings / re-invested business revenue - In-kind contributions - Various debt/equity financing instruments

Annex 1: Disease scoping

CEPI is drawing on the WHO R&D Blueprint and other processes being developed to identify dangerous and epidemic-prone pathogens. As figure 13 demonstrates, there is only a small convergence of pathogen priorities between different lists generated by different organizations operating in this space.

FIGURE 13: PATHOGEN PRIORITY LISTS BY DIFFERENT SOURCES (2016)



Sources: https://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Pages/CatA.aspx, http://www.vaccinefoundation.org, WHO R&D Blueprint

Disease scoping requires a pathogen prioritization methodology. Pathogen priority lists in Figure 13 consider different sets of criteria prioritization. Using lists of prioritised pathogens from WHO and Foundation for Vaccine Research a CEPI task team evaluated vaccines against 12 diseases (with filovirus and coronavirus each including more than one pathogen) on the basis of the following principles and assumptions:

- the pathogen has epidemic potential
- a vaccine has limited market potential
- a vaccine must be feasible (CEPI must demonstrate a measurable outcome in the next 1-2 years)
- preclinical research and Phase III trials are out of funding scope
- public health impact of having a vaccine available against a disease is taken into account

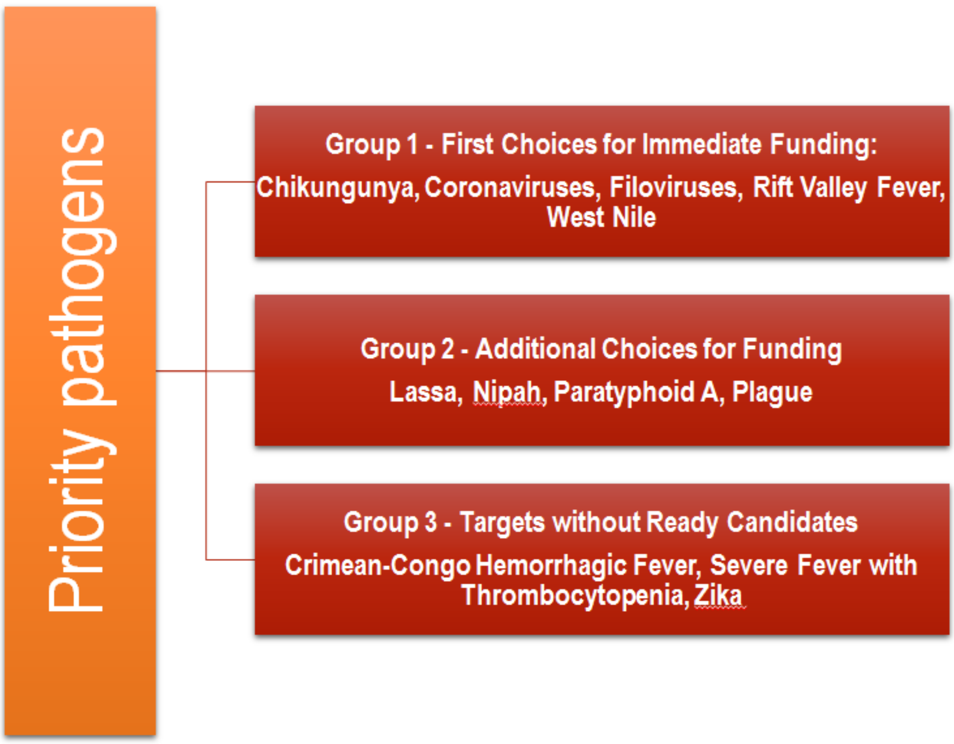
The primary set of criteria was feasibility of taking candidates developed and published by research laboratories, biotechs or vaccine manufacturers to GMP production, clinical testing and establishment of stockpiles and/or Phase III trials and licensure. Determination of feasibility depended on the following criteria:

- **Protection in a relevant animal model**: Protection in mice also scored but rated lower than protection in models closer to humans.
- **Evidence for a correlate of protection**: Preferably inferred from data in humans, but also counted if inferred from animal or natural history data.
- **A viable platform for vaccine manufacture exists**: Preferably more than one. If the proposed vaccine was accomplished by an important technological advance in vaccinology that could be applied to other vaccines its score was increased.

Secondary sets of criteria also evaluated potential disease impact and the possibility of spread from person to person or from one geographical area to another.

The results of scoring were grouped into three levels of recommendation for the 12 diseases evaluated: the highest five for which immediate investment would result in stockpiles of effective vaccines that could be expanded as needed; a second group of four for which vaccine development is clearly possible but which did not score as highly as the top four because of unresolved technical issues; and a third group for which no candidate is as yet ready for funding.

FIGURE 14: PRIORITY PATHOGENS ACCORDING TO TASK TEAM 1, SUBGROUP 1 RECOMMENDATIONS



It is worth noting that three diseases (West Nile Virus, Paratyphoid A and Plague) listed by TT1 SG1 were not part of the WHO priority pathogen list. The framework for prioritization and resulting recommendations were developed bearing in mind that these are interim and that they would need to be ratified or not by the CEPI Scientific Advisory Committee, once that is established.

Annex 2: Disease epidemiology and pipelines

Disease	Disease characteristics and epidemiology	Disease vaccine pipeline specifics
Chikungunya	Chikungunya fever, a Aedes mosquito transmitted disease caused by chikungunya virus (CHIKV) (an alphavirus), is an acute febrile illness characterized by severe, debilitating polyarthralgia, that often progresses to a chronic stage, with reports of over 60% of those affected suffering from joint pain three years after infection. The epidemic began in East Africa in 2004 spreading to the Indian Ocean Basin, India and Southeast Asia, where millions of cases have occurred. Since 2013 spread to 45 countries in the American with more than 1.7 million registered cases. Only a minority of cases are asymptomatic. The major symptoms are rash with polyarthralgia and arthritis. Mortality is low (case fatality rate 1:1000), but long-lasting sequelae in the form of incapacitating polyarthritis, particularly in the elderly. Neurological and cardiovascular complications also occur. An estimated one million cases of Chikungunya occur each year, mainly in urban settings and with high attack rates. (refer TT1, SG1) (NIPH Vax opp report 2016).	The most advanced candidates are live attenuated, VLP, measles vector and inactivated whole virus, but there are at least 21 projects including DNA plasmids, subunit and several other vectored vaccines, and there are hopes that induction of antibody should be protective. A live attenuated strain was taken into phase 2 by the US Army and produced good levels of antibody, although accompanied by transient arthralgia in 10% of vaccinees. The Army also briefly tested an inactivated vaccine. More recently, the Vaccine Research Center of NIH created a VLP vaccine and showed immunogenicity and safety in phase 2 trials. A biotech is reportedly moving forward with the VLP vaccine. A recombinant measles virus carrying the RNA for Chikungunya envelope has been in a successful phase 1 trial. Studies in animals suggest that passively administered and actively induced neutralizing antibody is protective and that although cellular responses may be useful in recovery from infection, antibody is a correlate of protection.
Middle East respiratory syndrome coronavirus (MERS-CoV)	MERS Co-V, an emerging infectious disease of growing global importance, has caused severe acute respiratory disease in 1626 people, resulting in 586 deaths (2012-2016). It has a high case fatality of 36%, it is transmissible from human to human, has a growing geographic distribution and a vaguely defined epidemiology. The most recent outbreak was in May 2015 in South Korea. Dromedary camels are the likely intermediate animal reservoir, and research to date indicates bats are the original host. (Modjarrad, 2016) (NIPH Vax opp report 2016)	A DNA vaccine against SARS expressing the S protein was put into a Phase I trial by the VRC. It elicited neutralizing antibodies after three doses as well as CD4+ T cell response. CD8+ responses were seen in a minority of subjects. Sinovac tested an inactivated virus vaccine. Fortunately, there are multiple other candidates besides those from the VRC. Prominent among them is a stable S trimer nanoparticle produced by Novavax, a plasmid DNA vaccine for the S protein produce by Inovio in collaboration with the GeneOne company in South Korea, which is in Phase 1 trial, and several vectored vaccines, including ones based on S or S1 expressed by adenoviruses, chimp adenovirus, measles, and MVA, all of which have shown immunogenicity in animals and some of which have also tested positively for protection. The organizations testing these vaccines are based in China, the UK, the US and Germany. It appears that neutralizing antibodies are a correlate of protection, with CD8+ T cells useful if infection takes place, and that multiple known manufacturing platforms are available.
Severe Acute Respiratory Syndrome (SARS)	SARS is a coronavirus, with patients presenting with acute and severe respiratory symptoms of fever, cough, and pneumonia. Alveolar damage occurs with inflammatory cell infiltrates. Mortality rate is between 10 - 50 %. During 2002-2003 outbreak in Asia and some non-Asian countries there were 8422 cases and 916 deaths. No outbreaks has occurred since and the outbreak strain appears to have been eradicated, however a few laboratory associated infections were seen in 2004. Human-to-human transmission was efficient in health-care setting but proved controllable through good infection control practices. (NIPH Vax opp report 2016)	
Ebola	Ebola virus is a member of Filoviridae family, and has five species: Zaire ebolavirus (EBOV), Sudan ebolavirus (SUDV), Taï Forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV). Transmission of Ebola virus to humans likely occurs through handling of infected chimpanzees, gorillas, monkeys, bats, antelopes and porcupines. Person to person transmission occurs through direct contact with body fluids from Ebola patients, corpses of deceased Ebola victims, and contaminated objects. Symptoms diffuse, with fever, headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal pain and bleeding or bruising. EBOV, SUDV and BDBV can cause large viral hemorrhagic fever disease outbreaks. The case fatality rate differs between the five species of Ebola virus, with EBOV showing up to 90% CFR. Since discovery of Ebola virus in 1976, the cumulative case number reported as at Dec 2015 is 31,048. (NIPH Vax opp report 2016)	One vaccine candidate (rVSV-ZEBOV) has demonstrated clinical efficacy in a Phase III trial in Guinea (NewLink Genetics, Merck Vaccines). The manufacturer applied for WHO Emergency Use Assessment Listing (EUAL) in Dec 2015. Gavi has agreed to purchase and stockpile 300,000 doses of the pre-licensed vaccine. In Oct 2015, WHO's Strategic Advisory Group of Experts on Immunizations (SAGE) concluded that available safety data for both cAd3-ZEBOV/ ChAd3-EBOZ (GSK/NIAID) and rVSV-ZEBOV vaccines indicate an acceptable safety profile in healthy adults. The Phase II/III trial to examine safety and efficacy of rVSV-ZEBOV and cAd3--ZEBOV initiated in Liberia had the Phase III component suspended due to low incidence. The cAd3-ZEBOV vaccine may also be used in a heterologous prime-boost strategy with a recombinant modified vaccinia Ankara (MVA) booster vaccine manufactured by Bavarian Nordic (MVA-BN-Filo). In Sierra Leone, Crucell is conducting a multi-staged Phase III study to assess safety and Immunogenicity of Ad26.ZEBOV and MVA-BN-Filo during implementation of stages 1 and 2 (EBOVAC-Salone). HHS, BARDA is supporting advanced development of this regimen. There are a number of prime-boost vaccine

		regimens in phases I and II. Five novel vaccines are in Phase I or intend to move to Phase I.
Marburg	Marburg hemorrhagic fever (termed Marburg HF or Marburg fever disease (MVD)) is a rare but severe hemorrhagic fever that can cause disease in both humans and non- human primates. The reservoir host of Marburg virus is the African fruit bat, Rousettus aegyptiacus. Transmission occurs by human contact with infected wild animals (monkeys, fruit bats) or their remains, e.g. by male mine workers working in bat-inhabited mines, or by direct contact with blood, body fluids and tissues of infected persons. Person to person transmission is enhanced by cultural practices and in under-protected communities and health care facilities. Marburg HF virus has a capacity to cause dramatic outbreaks with high fatality, the disease is characterized by abrupt presentation of severe headache and malaise, with a large proportion of patients developing severe bleedings between days 5 and 7. Fatal cases often present with bleeding at multiple sites. Case fatality rates vary from 25% to 80%. Marburg HF occurs as sporadic outbreaks in Africa, with confirmed cases reported in Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, Angola, and South Africa. Sporadic export cases from Africa (e.g. Uganda) to EU and US also reported. The total cumulative number of cases reported worldwide since the virus was first reported in 1967 is 466, of which 373 died. The last major outbreaks occurred in DRC in 1998-2000 (154 cases), Angola in 2004-2005 (252 cases) and Uganda in 2012 (15 cases). (NIPH Vax opp report 2016)Rift Valley Fever: Veterinary vaccines already exist for this disease, based on antibody induction. Multiple live and inactivated candidates have already been tested in humans so the task is to complete development of one or more for widespread use.	A number of developers (NIAID, Profectus, AgilVax, Integrated Biotherapeutics) have vaccine candidates against Marburg in Phase I, with three of the four based on DNA technology. Vaccine candidates vectored by recombinant vesicular stomatitis virus are also in Phase I or preclinical. The Phase I candidates are multi-valent filovirus vaccines for Ebola and Marburg. Multiple preclinical candidates show promise and have demonstrated protection in NHPs, most of these approaches focus on the MARV GP.
Rift valley fever virus (RVFV)	RVFV is classified as a Phlebovirus in the family Bunyaviridae, and is transmitted to humans by a mosquito vector. Over 30 mosquito species are known to be able to carry RVFV. Another very important source of transmission to humans is contact with diseased animals (such as during slaughter) and animal products, with outbreaks reported among humans often originating from a livestock outbreak. RVFV causes fever, headache, dizziness, nausea, weakness, and myalgia in humans, with progression to severe disease in a minority of patients (usually around 1%) and case fatality rates of 4-44% among severe cases. Severe symptoms include retinitis, encephalitis, and hemorrhagic manifestations. Neurological disorders can also develop. Outbreaks have been reported since 1930s with up to 200,000 cases. The largest outbreak was in Egypt (1977), followed by an outbreak three sub-Saharan countries (1997-1998) with the most recent this century outbreak in Saudi Arabia and Yemen. (refer TT1, SG1; NIPH Vax opp report 2016)	A RVFV vaccine based on an inactivated Entebbe virus strain (NDBR-103) has been available for use in humans (mainly laboratory workers) since the 1960s, and is produced by the U.S. government. The Salk Institute, Government Service Division, produced a second generation, updated version of this vaccine to meet improved standards of production (TSI-GSD 200). The vaccine has been tested in trials for more than 20 years and shows good safety and efficacy, but requires a three-dose schedule and a booster vaccination and will likely not be pursued for use in an outbreak setting. Therefore, continued development of other vaccine candidates is warranted. RVFV has been well characterized, and several relevant animal models exist for testing new vaccines and therapies. There are many vaccine candidates that have shown promise in preclinical models and could be moved into Phase I trials. The live attenuated RVF MP-12 vaccine has been shown to be safe and immunogenic when given as a single dose in Phase I and II trials, and could be further investigated in clinical Phase II/III trials. While live, attenuated viruses most effectively elicit protective immune responses, development of subunit vaccines or inactivated virus vaccines should be pursued in parallel due to an assumed improved safety profile.
Lassa fever	Lassa fever (LF) virus (LASV) is a member of the Arenavirus family. LASV occurs throughout West Africa and is endemic in Sierra Leone, Liberia, Guinea, and Nigeria. Smaller numbers of cases have been reported Cote d'Ivoire and Burkina Faso, with serological evidence of infection in Togo and Benin. Eastern Sierra Leone has the highest incidence in the world. The main reservoir is the rodent Mastomys natalensis (known as the "multimammate rat"). Transmission of LASV to humans is through direct contact between rodent and humans living in West Africa villages through ingestion or inhalation of virus via Mastomys rodent's urine and droppings. Person to person transmission occurs through close contact with infected blood, tissue, or secretions of Lassa-infected individual, often from patients hospitalized with Lassa fever or in households. Symptoms of LF include fever, malaise, weakness, and headache. In 20% of people, disease may progress to more serious symptoms including hemorrhaging, respiratory distress, vomiting and shock. The case	There are several preclinical LF vaccine candidates currently in development. There are a number of recombinant gene-based vaccines in development including those utilizing alphavirus, vesicular stomatitis (VSV), vaccinia, and chimeric yellow fever live virus vectors as well as a self-assembling vaccine. The furthest in development is a recombinant VSV-vectored vaccine which expresses the G protein on its surface. This vector is similar to the one that has been used for the Ebola recombinant VSV vaccine candidate which has shown favorable safety, immunogenicity and efficacy results. This LF vaccine provided protection in non-human primate challenge models as well as provided cross-clade protection in guinea pigs. Both the G and N proteins have been found to protect in a NHP challenge model which is believed to be the most relevant animal model based on its correlation with human clinical disease for viral hemorrhagic fevers. There is a need to better understand

	fatality rate is approximately 1%; however, case fatality rates during epidemics can be as high as 50%. The number of LF infections in West Africa ranges from 100,000 to 300,000 annually and approximately 5000 deaths each year but these numbers are believed to be underestimated due to limited systematic disease surveillance. (refer TT1, SG1) (NIPH Vax opp report 2016)	mechanisms and correlates of protection in humans. All three candidates which have shown 100% protection in NHP models could move forward to Phase I clinical trials. No human vaccine clinical trials have been conducted to date.
Nipah virus	Nipah virus is a metapneumovirus that is carried by fruit bats. Bangladesh is the major site of human infections, but disease does occur in Malaysia, Singapore, the Philippines and India. There appears to be considerable cross-immunogenicity with the related Hendra virus. Bats can infect pigs, from which virus can pass to humans, or humans can be directly infected. The nature of human-to-human transmission is not clear but requires close contact perhaps mediated by droplets, fomites, intimate contact with body secretions or a combination of these elements. Nipah virus is excreted in saliva, nasopharynx and urine, and human to human infection does occur. Human cases typically present with abrupt onset of fever, headache, dizziness, and vomiting. Neurological signs include reduced levels of consciousness, segmental myoclonus, areflexia, hypotonia, and abnormal doll's eye-reflex which develop in these individuals within a week of fever onset. Encephalitis is a prominent clinical feature and may recur. Respiratory disease is also prominent and the mortality is about 40%. (refer TT1, SG1; refer Satterfield 2016)	Passive antibodies have been shown to protect against Nipah, so the correlate of infection is presumably neutralizing antibody. There are numerous candidates, most based on the VSV vector, but also canarypox, measles, venezuelan equine encephalitis and Newcastle disease virus. The inserted Nipah genes are for the F or G proteins. All seem to work in animal models, and a Hendra G subunit vaccine gave cross-protection against Nipah. A biotech called Zoetis is working with the US Army, presumably to develop a Nipah/Hendra vaccine. It is likely that two candidates, one based on virus-like particles containing G, F and M proteins, and the other based on a Japanese measles vector, have moved into phase 1, but this is not confirmed from the published literature.
Crimean-congo Hermorrhagic fever virus (CCHF)	CCHF is a bunyavirus carried by Hyalomma ticks. More than 30 outbreaks with a total of >10,303 cases have been reported in Southeast Europe, Asia, the Middle East, and Africa since the discovery of the virus in the 1940s. In Turkey it is currently a major problem, where the largest outbreak occurred from 2002-2009, with 4,431 cases. Recently it has also been found in Greece and Bulgaria, where it is endemic. It has a high mortality ranging between 15 and 70%, and can be transmitted from human to human by contact with infected blood and body fluids or needlestick. Infected animals may also be a source of contamination. (refer TT1, SG1; NIPH Vax opp report 2016)	An inactivated vaccine made in mouse brain has been available but its efficacy is poorly documented and may not give lasting protection. Subunit vaccine based on structural glycoproteins failed to protect in immunocompromised mice although it produced neutralizing antibodies. An inactivated whole virus vaccine did not protect mice, nor did a vaccine based on the nucleoprotein of the virus. However, an MVA vector expressing the viral glycoproteins was recently shown to protect mice against an intradermal challenge. At this stage it must be concluded that vaccine development is in its infancy and animal models are not optimal.
Severe fever with thrombocytopaenia syndrome (SFTS)	The first outbreak was reported in China in 2009. Between 2011 – 2014, >3500 cases have been reported in China, with an average case fatality rate of 7.8%. Outbreaks have also occurred in Japan and South Korea. Two cases of a very similar virus, named Heartland virus, were reported in the USA in 2012. SFTS epidemics have shown a seasonal distribution in China, with peak incidence in May to July. (NIPH Vax opp report 2016)	No projects currently in the pipeline
Zika virus	Zika virus is a Flavivirus, most infections are asymptomatic (60-80%). Disease symptoms are usually mild and self-limiting after 2-7 days. Most commonly fever, macular or papular rash, arthralgia, muscle pain, joint pain, headache, pain behind the eyes and conjunctivitis. In addition, there is suspected association of ZIKV infection with significant increase in congenital anomalies (mainly microcephaly), Guillain-Barré syndrome and other neurological and autoimmune disorders in areas of recent ZIKV outbreaks (French Polynesia and Brazil). Causal relationship of this is under investigation. Before 2007, viral circulation and a few outbreaks occurred in tropical areas of Africa and some areas of Southeast Asia. From 2007 to 2015, outbreaks on seven of the islands of the Pacific region occurred, with a major outbreak and spread in the Americas from 2015. In Brazil since May 2015, there have been between 440,000 to 1,300,000 confirmed cases, with 2972 microcephaly cases identified. (NIPH Vax opp report 2016)	There are several vaccines under pre-clinical development (6) including inactivated whole virus, live attenuated (eg YF17D chimera), and DNA plasmid based. One DNA vaccine (GLS 57-000) + an electroporation device from Inovio US Pa, has recently received US FDA Clearance to move to a Phase I Human Trial by Q3 2016. Another DNA vaccine from the US NIH and one inactivated vaccine will follow by Q3/4 2016. These vaccines elicit immune responses in naïve individuals and some have evidence of protection in rodent models. While WHO is working on a Target Product Profile, the market for a Zika vaccine is speculative based on other comparable Neurotropic Flaviviruses, e.g., West Nile.

Annex 3: List of CEPI members

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Annex 4: CEPI Board members

BOARD MEMBERS

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4. Tore Godal, Special Adviser on Global Health, Section for Global Initiatives, Ministry of Foreign Affairs, Norway
5. Ruxandra Draghia-Akli, Deputy director-general of DG RTD, European Commission
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16. Joanne Liu, International President, Medecins sans Frontieres
17. Peter Piot, Director of the London School of Hygiene and Tropical Medicine
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